TECHNICAL APPENDIX

HPV-ADVISE

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1 Model structure

1.1 Demography

The population modeled represents the heterosexual population of Canada. For simplicity, we assume an open but stable population due to the slow growth rate of the Canadian population [8]. Ten year old individuals enter the population (with a 1:1 male to female ratio) at a rate η chosen to balance Canadian age-specific death rates $\mu_g(a)$. The equilibrium age distribution of the population is found by running the demographic model (i.e. model without HPV infection) for 500 years. Individuals younger than 10 years old are not included in the model because they have a very low prevalence of sexually acquired HPV infection. See details on demographic parameters in Section 2.2.1.

1.2 Sexual behaviour and HPV Transmission

1.2.1 Sexual activity levels

Upon entry in the simulated population, 10-year-olds are assigned to a level of sexual activity from low ($l = 0$) to high ($l = 3$). Please refer to 2.1.2 for the prior and posterior distributions of the fractions of individuals Φ_l assigned to each level. 10-year-old girls are assumed to begin sexual activity at a rate $\varphi_l(a)$ that depends on their age and level of sexual activity. A specific partner acquisition rate $\theta_{g,l}(a)$ (i.e., number of new partner acquisitions per year) is then attributed to each sexual activity level by age (Refer to 2.2.2 for details and parameter values).

1.2.2 Partnership formation and separation process

The model is based on a stochastic pair formation and separation process, which represents the underlying structure of the sexual contact pattern. We model sequential monogamous stable and casual partnerships. Concurrent partnerships are not taken into account.

The partnership formation and separation process is driven by females as illustrated in Figure A1. Each woman has an associated age and level of sexual activity specific rate of either forming a new partnership if they are single $\varsigma_l(a)$, or separating $\sigma_l(a)$ if they are currently involved in a stable partnership. When a new partnership is formed, the male

partner is selected according to a mixing matrix $\boldsymbol{\Omega} = [\Omega_{al,a'l'}]$, which reflects the preferences of an individual of age a and level of sexual activity l for individuals of age a' and level of sexual activity l' (see next section for more details on the mixing matrices). If no male partner is available in the selected category, no partnership is formed. All newly formed partnerships have an age and level of sexual activity specific probability of being stable $\psi_l(a)$ (see details and parameter values in Section 2.2.2).

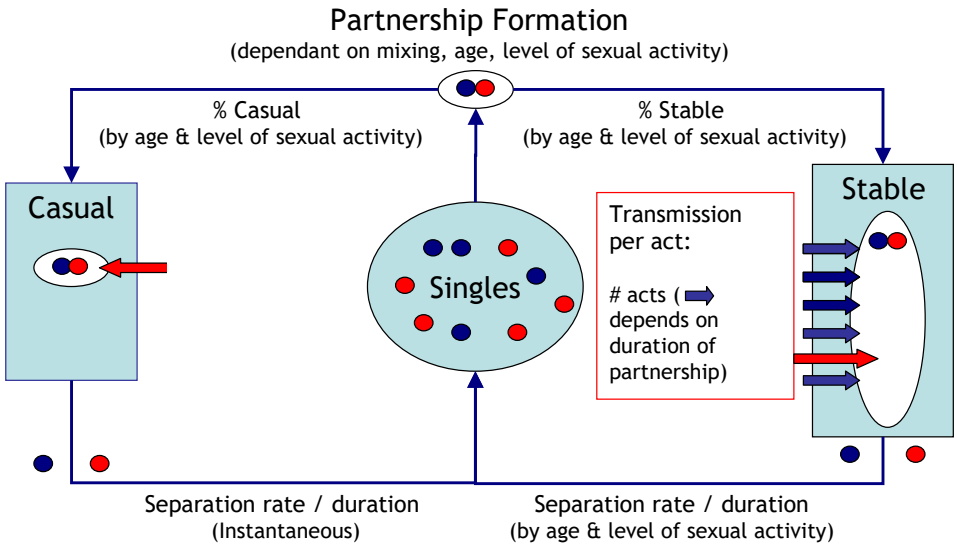


Figure A1. Partnership formation and separation process. Plain red circles represent infectious individuals, and red arrows represent HPV transmission. Casual partnerships occur instantaneously, whereas stable partnerships have a duration dependent on age and level of sexual activity.

The partnership formation rates of single females $\varsigma_l(a)$ is derived from the partner acquisition rates $\theta_{g,l}(a)$ and the age and level of sexual activity specific proportions of stable partnerships $\Psi_l(a)$ taking into account the proportions of individuals not available for partnership formation as follows:

$$\varsigma_l(a) = \frac{\theta_{g,l}(a)}{\left(1 - \Psi_l(a)\right)} \tag{1.1}$$

Where the indices g, a and l represent gender, age and sexual activity level, respectively (refer to Table A26 for the list of all symbols).

1.2.3 Contact/Network structure

Mixing by sexual activity level

The sexual activity mixing matrix, $\mathbf{\Gamma} = [\Gamma_{l,l',g}]$, defines the probability that an individual of gender g and level of sexual activity l forms a partnership with someone of the opposite gender in level of sexual activity l'. The matrix is computed as follows [9]:

$$\Gamma_{l,l',g} = \frac{W_{l,l',g} \sum_{a'} \left\{ N_{l',g'}(a') \cdot \theta_{g',l'}(a') \right\}}{\sum_{l'} \left\{ W_{l,l',g} \sum_{a'} \left[N_{l',g'}(a') \cdot \theta_{g',l'}(a') \right] \right\}} \tag{1.2}$$

Where $N_{l,g}(a)$ is the number of individuals of gender g, sexual activity level l and age group a, $\theta_{g,l}(a)$ is the mean rate of sexual partner acquisition for gender g, sexual activity level l and age group a, and $W_{l,l',g}$ defines a set of weights corresponding to the preference of an individual of gender g and sexual activity level l for someone of the opposite gender with sexual activity level l' (preference matrix).

Detailed data on each element of the mixing matrix by degree is rarely available and therefore, the preference matrix is often summarized by the assortative degree parameter κ (refer to 2.2.2). The preference matrix is defined as follows [9]:

$$W_{l,l',g} = \begin{cases} \kappa, \text{ if } l = l' \\ 1, \text{ if } l \neq l' \end{cases} \tag{1.3}$$

Where $\kappa > 1$ represents assortative mixing; $\kappa = 1$ is proportionate mixing and $\kappa < 1$ disassortative mixing.

Mixing by age

Similarly, the age mixing matrix, $\mathbf{\Lambda} = [\Lambda_{a,a',l,g}]$, defines the probability that an individual of gender g in age group a and sexual activity level l forms a partnership with someone of the opposite gender in age group a'. This age mixing matrix is thus level of sexual activity-specific and was derived from observed data as explained in Section 2.2.2.

Global mixing matrix

The global mixing matrix, $\boldsymbol{\Omega} = [\Omega_{al,a'l'}]$, is the product of the mixing matrix by age and by sexual activity level:

$$\Omega_{al,a'l'} = \Gamma_{l,l',g=1} \cdot \Lambda_{a,a',l,g=1} \tag{1.4}$$

Because the partnership formation and dissolution process is driven by females, we computed only female matrices, $g = 1$.

1.3 Natural History of HPV-related diseases

1.3.1 Squamous cell carcinoma

HPV-ADVISE models the following 18 HPV genotypes individually: 16, 18, 6, 11, 31, 33, 45, 52, 58, 35, 39, 51, 56, 59, 66, 68, 73, and 82, and independently. That is, we assume that infection with a given genotype does not protect against infection or alter disease progression with the other genotypes (i.e. no partial or mutual exclusion). The infection status (susceptible, infected, and immune) of each individual is type-specific and, therefore, an individual can be infected with multiple genotypes at the same time. This assumption is particularly important as co-infections are present in about 15% of infected individuals[10-15]. Infected women can either clear the infection and return to immune/susceptible status or remain infected and progress in the model to more severe stages of cervical intraepithelial lesions of grade 1 (CIN1), 2 (CIN2) or 3 (CIN3), and invasive squamous cervical cancer (SCC) of stage 1 (localized), stage 2 (regional) or stage 3 (distant). Women with CIN may also regress to a less severe stage or clear the infection and directly return to susceptible/immune status. For transmission probabilities and clearance, progression and regression rates refer to Section 2.2.3.

1.3.2 Anogenital warts

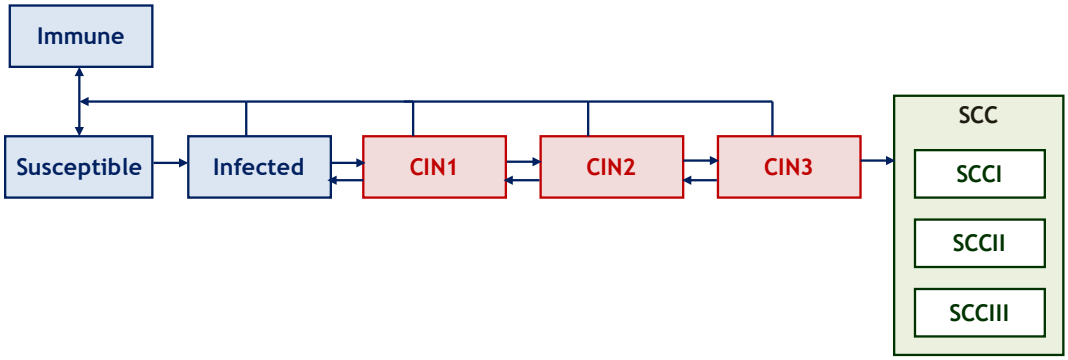
In HPV-ADVISE, individuals have a joint probability of developing and being diagnosed with anogenital warts (AGW) or clearing their infection. Individuals can experience multiple episodes of AGW through recurrence of a persistent infection, re-infection with a previously cleared HPV-type or infection with a new HPV-type.

1.3.3 Other HPV-related diseases

In HPV-ADVISE, infected individuals have a gender- and type-specific probability of progressing towards cervical adenocarcinoma, and cancers of the anus, oropharynx,

vulva, vagina, and penis, and a gender- and type-specific time of progression from persistent infection to cancer.

a)



b)

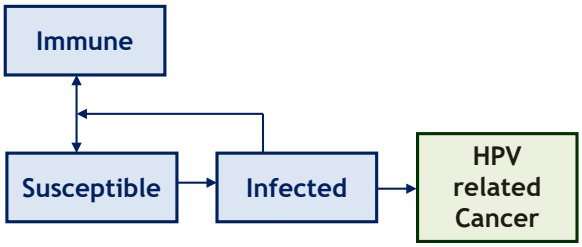


Figure A2. Flow diagram of a) the natural history of HPV infection and squamous cell carcinoma, and b) other HPV-related cancers (cervical adenocarcinoma, and cancers of the anus, oropharynx, vulva, vagina, and penis). The mutually exclusive compartments represent the different HPV epidemiological states. Arrows represent the possible HPV-type specific transitions between these states for each individual. Arrows represent the possible HPV-type, age, and gender specific transitions between these states for each individual.

1.4 Screening and treatments

1.4.1 Screening behaviour levels

Upon entry in the simulated population, 10-year-old females are assigned to a level of screening behavior based on the interval between two routine screening tests. The levels of screening behaviour range from a short interval between two routine screening tests ($S = 0$) to never having been screened ($S = 4$). Please refer to section 2.2.4 for the distribution of women assigned to each level of screening behaviour.

In HPV-ADVISE, 10-year-old women are assumed to begin cervical cancer screening at an age-specific rate. A specific screening rate (i.e. number of routine cervical screening

test per year) is then attributed to each screening behaviour level (refer to 2.1.4 for details and parameters values).

1.4.2 Screening performance for the detection of cervical lesions

Depending on their true health state (Figure A2), women tested using cytology or colposcopy are given probabilities of being diagnosed with different results. For example, a woman with CIN1 has probabilities of 41%, 12%, 29% and 18% of having a normal, ASCUS, LSIL, or HSIL cytology result, respectively. Refer to Section 2.2.4 for the health state-specific probabilities and references for parameter values. In addition to the probability of being detected by screening, women with SCC also have a probability of developing symptoms and being diagnosed outside of the screening program. Refer to Table A18 of Section 2.2.3 for details, parameters values and references.

1.4.3 Management of women with abnormal screening results

Algorithms for the management of women with abnormal cytology and histology results were developed in accordance with the most recent Canadian guidelines[16-18] and were validated by Canadian gynecologists and screening experts to reflect current practice in Canada (Drs MH Mayrand, F Coutlée and E Franco). These algorithms are independent of age and are a function of cytology and histology results.

Management of women with ASC-US and LSIL. Women with a cytology result of atypical squamous cells of undetermined significance (ASC-US) or low–grade squamous intraepithelial lesions (LSIL) are followed-up with repeat cervical cytological testing at a 6-month interval until 2 consecutive negative tests are obtained. Given that some guidelines also recommend a colposcopic examination for women with LSIL, we assumed that a small proportion of these women would be referred directly for colposcopy/biopsy. Women with ASC-US or more severe cytologic abnormality on a repeat cytology test are referred to colposcopy/biospy for histological diagnosis. Depending on the colposcopy/biospy results, women can either return to routine screening (normal result), be monitored with repeat cervical cytology testing every 6 months for 2 years (CIN1) and return to routine screening after 2 consecutive normal results or be treated (CIN1 persistent for 2 years, CIN2+). The treatment of CIN can fail and have no impact on the natural history of the disease or be successful. If the treatment is successful, the lesion might clear but the woman remains infected, or the lesion and the infection might clear. The treatment of SCC

can also fail and lead to death (see 5-year survival rates in Section 2.2.3). Finally, although lost to follow-up can occur at every step of the algorithm, to simplify the model and because detailed data on lost to follow-up at every step were not available, we used a lesion-specific global estimate of the proportion of women lost throughout the follow-up.

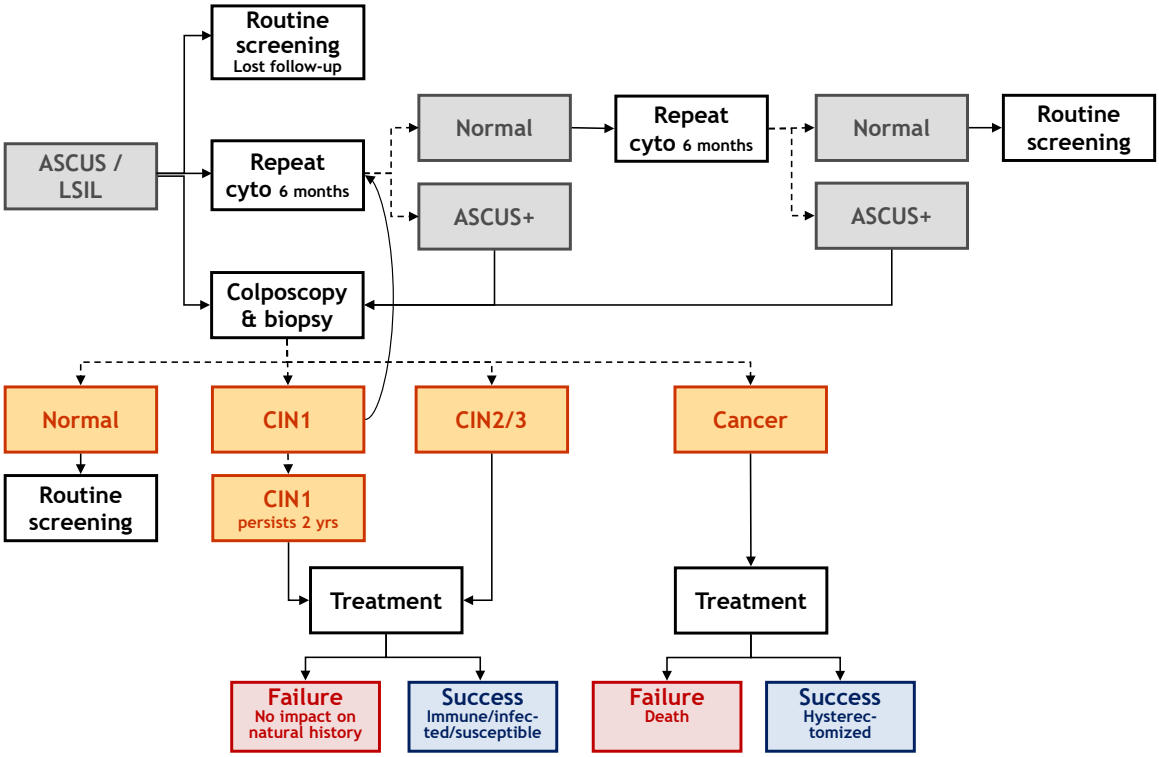


Figure A3. Management of women with ASC-US and LSIL. Gray boxes represent cytological results, white boxes represent screening, diagnosis and treatment procedures, orange boxes represent the colposcopy results and red and blue boxes represent treatment failure and success, respectively. Solid lines represent model parameters whereas dashed lines represent model outputs based on the natural history of disease.

Management of women with HSIL, ASC-H and SCC. Women with high-grade squamous intraepithelial lesions (HSIL), atypical squamous cells-cannot exclude HSIL (ASC-H) and squamous cell carcinoma (SCC) are directly referred to colposcopy/biopsy for histological diagnosis. Women who obtain a normal or a CIN1 result at the colposcopic exam are monitored using repeat colposcopy every 6 months for 1 year. After two consecutive normal results, women are returned to routine screening. However, if CIN1 persists for 1 year or if lesions ≥ CIN2 are diagnosed, women are treated. Outcomes of treatment are similar to those previously described.

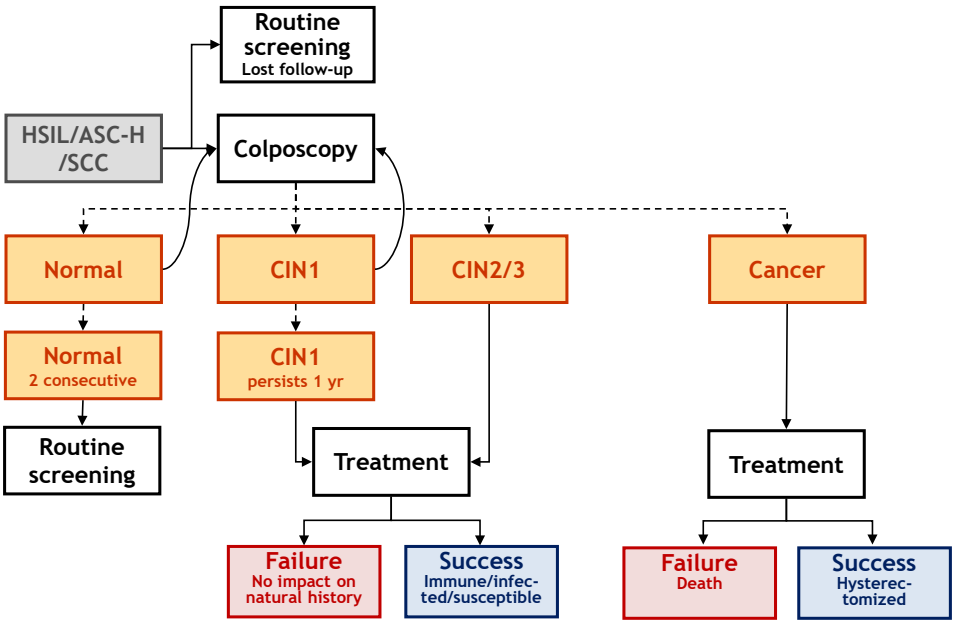


Figure A4. Management of women with HSIL and ASC-H. Gray boxes represent cytological results, white boxes represent screening, diagnosis and treatment procedures, orange boxes represent the colposcopy results and red and blue boxes represent treatment failure and success, respectively. Solid lines represent model parameters whereas dashed lines represent model outputs based on the natural history of disease.

1.5 Men who have sex with men (MSM) model

A separate module was built for modeling HPV associated diseases in MSM. This model estimates a disease-, gender- and age-specific fraction of incidence of HPV associated diseases in the male population that are attributable to MSM. The incidence among MSM is then added to the predicted incidence for heterosexual men.

When assessing the impact of vaccination strategies, the following assumptions are made. It is assumed there is no impact on MSM when vaccinating girls only. When boys are vaccinated in addition to girls, the direct and indirect impact of vaccination on MSM is calculated. For the direct impact, vaccine efficacy for heterosexuals and MSM is assumed to be the same. For the indirect impact, age- and type-specific herd effect over time among MSM is assumed to be the same as among heterosexuals.

1.6 Economic component

The model attributes, over time, direct medical costs and Quality-Adjusted Life-Year (QALY) weights to model outcomes (e.g., Pap tests, diagnosed lesions, AGW, cancer, mortality) to estimate the cost-effectiveness of HPV vaccination and cervical cancer screening. See Brisson et al.[19] for parameter values.

2 Model Parameterization

The calibration procedure is used to identify multiple parameter sets that simultaneously fit highly-stratified sexual behaviour, natural history, and screening data. Table A1 in Section 2.1 presents the data sources used for calibration and Table A2 in Section 2.2 lists all the model parameters that have been derived through calibration. Section 2.2 describes in details the prior ranges and the posterior parameter sets for each parameter.

2.1 Calibration procedure

The calibration procedure has been described briefly in the main article and extensively in prior publications[20,21] : 1) prior distributions are defined for each of the 88 calibrated model parameters (Table A2) (min.–max. values for each parameter are derived from the literature); 2) thousands of different combinations of parameter values are drawn from the prior distributions using Latin Hypercube sampling; 3) parameter sets are qualified as producing a "good fit", and included in the posterior parameter sets, if the associated model predictions fall simultaneously within pre-specified targets (ranges) of the observed sexual behavior, natural history, and screening data described in Table A1; 4) posterior parameter sets are cross-validated by comparing model predictions with observed epidemiological data not used during the fitting procedure.

We purposely used uniform distributions because the data and evidence used for our priors were scarce. It was therefore very difficult to define informed prior distributions other than a uniform between a maximum and minimum found in the literature. Given that we are fitting to data, using a uniform distribution instead of another distribution (that would span the same range) would make little difference on the values of the parameter sets that fit the data. Obviously, having more information to inform the prior distributions would have facilitated our search for suitable parameter sets fitting the data, as our search would have been more efficient and less computer intensive

We performed the calibration procedure in multiple steps given 1) the large number of model parameters and target points and, 2) fitting the incidence of squamous cell carcinoma requires a larger population (to reduce stochasticity) than infection or sexual behavior. Hence, we performed the calibration in four steps:

1) *Sexual behavior, Screening debut and High oncogenic risk HPV-type prevalence:* The goal of the first step was to estimate the values for the sexual behavior parameters, screening debut and the parameters influencing the transmission and clearance of high oncogenic risk HPV-types (HR-HPV) (57 parameters). To do so, we sampled 105,800 parameter sets using Latin Hypercube. Simulations were performed using a population of 56,450, the number of runs per simulation was 1, and the duration of a run was 100 years. A total of 66 parameter sets fell within the 302 pre-specified target points for sexual behavior (Percent that ever had sexual intercourse, Number of partners in past 12 months and Percent in stable partnership), screening debut (Proportion of women ever screened) and prevalence of high oncogenic risk HPV-type (Prevalence of HPV-16, HPV-16/18, HR-HPV, HR cross-protective types (HRC-HPV) and HR non cross-protective types (HPV-HRNC)) (Table A1).
2) *HPV-6 and HPV-11 prevalence*: The objective of step 2 was to find parameter values for HPV-6 and HPV-11 transmission probabilities and clearance rates (4 parameters). For each of the 66 parameter sets identified in step 1, we re-sampled 100 new combinations by varying the remaining 31 parameters not directly involved in step 1. The number of individuals in the population was 56,450, the number of runs per simulation was 2, and the duration of one run was 100 years. As we did not want to over-represent one specific region of the parameter space identified in step 1, we only selected the first parameter set that simultaneously fell within the 302 and 24 target points for step 1 and step 2 (HPV-6/11 prevalence (Table A1)), respectively. It is important to note that at each step of our forward selection process of model parameter values, the selected sets needed to fall within all previous target points in addition to the ones being evaluated. This is important as the natural history parameters can have an impact on the prevalence of infection, and the final posterior parameter sets were required to fit all target points simultaneously. A total of 52 parameter sets fell within the 326 pre-specified targets for step 1 and 2.

3) Positivity of HPV types in CIN1, CIN2/3 and SCC, distribution of cytology results (negative, ASC-US/LSIL, HSIL+) and incidence of ASC-US/LSIL and HSIL: The objective of step 3 was to parameterize the progression and regression rates of the natural history of SCC (27 parameters). We calibrated all natural history parameters in one stage as they are closely correlated with one another. To do so, we repeated the forward selection process described in step 2 multiple times for each parameter set until one fit was found or we reached a total of 5000 samples. The number of individuals in the population was 112,900, the number of runs per simulation was 10, and the duration of one run was 100 years. A total of 10 parameter sets fell within the 614 pre-specified targets for steps 1-3.
4) Incidence of SCC: We calibrated the progression from CIN3 to SCC (2 parameters) using Least Squares. For each of the 10 parameter sets fitting all previous target points, we sampled multiple progression rates to SCC and selected the 50 best fitting combination. The number of individuals in the population was 169,350, the number of runs per simulation was 10, and the duration of one run was 100 years.

We calibrated the age- and gender-specific proportion of HPV-6/11 leading to an AGW consultation separately because these parameters have no influence on the other natural history targets. For each of the 50 parameter sets from steps 1-4, we identified the AGW parameter values that best fit Canadian billings data[22], using Least squares.

We also calibrated the age-, gender- and type-specific incidence of adenocarcinoma, and cancers of the vulva, vagina, anus, penis, and oropharynx separately. For each of the 50 parameter sets from steps 1-4, we estimated the parameter values that best fit Canadian incidence data and HPV-type distribution[23-26], using Least squares.

Given that the modeled population is heterosexual, we estimated the fractions of the disease burden attributable to MSM and adjusted the calibration targets accordingly.

In summary, of 285,000 different combinations of parameters sampled (corresponds to 1,850,000 runs and $2x10^{13}$ person-years simulated) from the prior parameter distributions, 50 parameter sets produced model results within the 782 pre-specified targets. Table A1 presents the data sources used for calibration and Table A2 lists all model parameters that have been derived through calibration. Section 2.2 describes in details the prior

ranges and the posterior parameter sets found for each parameter. Section 2.3 shows examples of model fit to behavior, screening and epidemiological data. Section 2.4 compares model results obtained using the 50 fitting parameter sets with observed data not used in the calibration procedure (model validation). Section 2.5 model predictions of vaccination impact obtained using the 50 fitting parameter sets with surveillance data (mode predictive validation). Finally, Section 2.6 explains how targets were defined.

Table A1. Description of calibration data

	Stratification	Ref	Targets Points
Sexual Behavior			
Percent that ever had sexual intercourse	Age (15, … 24, [25-29], …, [45-49]yrs); Gender ($g \in \{1,2\}$)	[27]	60
Number of partners in past 12 months	Age ([15-19], …, [30-34], [35-49]yrs); Gender ($g \in \{1,2\}$)¥	[27]	98
Percent in stable partnership	Age ([15-24], …,[50-59]yrs); Sexual Activity Level ($l \in \{0,1,2\},\ l \neq 3$)	[28,29]	30
Natural history			
Prevalence of HPV-16¶	Age ([20-24] & [25-29]yrs); Sexual Activity Levels ($l \in \{0,1,2\},\ l \neq 3$)	[1,2]	12
Prevalence of HPV-16/18¶	Age ([20-24] & [25-29]yrs); Sexual Activity Levels ($l \in \{0,1,2\},\ l \neq 3$)	[1,2]	12
Prevalence of HPV-6¶	Age ([20-24] & [25-29]yrs); Sexual Activity Levels ($l \in \{0,1,2\},\ l \neq 3$)	[1,2]	12
Prevalence of HPV-6/11¶	Age ([20-24] & [25-29]yrs); Sexual Activity Levels ($l \in \{0,1,2\},\ l \neq 3$)	[1,2]	12
Prevalence of HPV-HR¶	Age ([15-19], …, [50+]yrs); Sexual Activity Levels ($l \in \{0,1,2\},\ l \neq 3$)	[1,2,6]	48
Prevalence of HPV-HRC¶	Age ([20-24] & [25-29]yrs); Sexual Activity Levels ($l \in \{0,1,2\},\ l \neq 3$)	[1,2,6]	12
Prevalence of HPV-HRNC¶	Age ([20-24] & [25-29]yrs); Sexual Activity Levels ($l \in \{0,1,2\},\ l \neq 3$)	[1,2,6]	12
Positivity of HPV types in CIN1	HPV-16,18,6,11,HRC¥,HRNC§	[30]	12
Positivity of HPV types in CIN2/3	HPV-16,18,6,11,HRC¥,HRNC§	[30]	12
Positivity of HPV types in SCC	HPV-16,18,HRC¥,HRNC§	[31]	8
Incidence of SCC	Age ([20-24], …, [60-64]yrs)	[3-5]	18
Incidence of AGW consultations	Age ([15-19], …, [60-64]yrs) Gender ($g \in \{1,2\}$)	[22]	18
Incidence of cervical adenocarcinoma	Age ([0-39], [40-59], [60-69], [≥70]yrs) HPV-16, 18, 31, 33, 45 ,52, 58	[23] *	28
Incidence of anal cancer	Age ([0-39], [40-59], [60-69], [≥70]yrs) Gender ($g \in \{1,2\}$) HPV-16, 18, 31, 33	[23,24,27,32]	32
Incidence of oropharyngeal cancer	Age ([0-39], [40-59], [60-69], [≥70]yrs) Gender ($g \in \{1,2\}$) HPV-16, 18, 33	[23,26,27,33]	24

Incidence of vulvar cancer	Age ([0-39], [40-59], [60-69], [≥70]yrs) HPV-16, 18, 31, 33, 45	[23,24]	20
Incidence of vaginal cancer	Age ([0-39], [40-59], [60-69], [≥70]yrs) HPV-16, 18	[23,24]	8
Incidence of penile cancer	Age ([0-39], [40-59], [60-69], [≥70]yrs) HPV-16, 18, 31, 33, 45	[23,25,27,33]	20
Screening			
Proportion of women ever screened	Age ([20-24], …, [60-64]yrs)	[27]	18
Distribution of cytology results (negative, ASC-US/LSIL, HSIL+)	Age ([25-29], …, [65-69]yrs); Screening behaviour levels $S \in \{0,1,2,3\},\ S \neq 4$)	[5,7]	216
Incidence of ASC-US/LSIL	Age ([20-24], ..., [60-64], [65+]yrs)	[5,7]	20
Incidence of HSIL	Age ([20-24], ..., [60-64], [65+]yrs)	[5,7]	20
Total number of data points			782

¶. Among sexually active individuals; HR=High oncogenic risk types; HRC= HR cross-protective types: 31, 33, 45, 52, 58; HRNC= HR non cross-protective types: 35, 39, 51, 56, 59, 66, 68, 73, 82. ¥. We were unable to fit the % of boys with less than 1 partner in the last year in the 15-19 age group (mainly because of age-specific mixing where females are more likely to choose male partners older than them). * Personal communication Dr. Gary Clifford, IARC, CliffordG@iarc.fr

2.2 Parameters

Table A2. List of model parameters

Parameters	Stratification	Parameter values
Demography (Section 2.2.1)		
Sex ratio at birth	none	
Mortality rates* (per person-year)	Age (a = [10-14], …, [84-89], [90+]yrs); Gender ($g \in \{1,2\}$)	Table A3
Hysterectomy rates for other reasons (per person-year)	Age (a = [10-19], [20-44], [45-54], [55-64], [65+]yrs)	Table A4
Sexual Behavior (section 2.2.2)		
Proportion of individuals in sexual activity levels	Sexual Activity Levels ($l \in \{0,1,2,3\}$); Gender ($g \in \{1,2\}$)	Table A5/ Figure A5
Partner acquisition rates (per person-year)	Age (10,… 19, [20-24], …, [50+]yrs); Sexual Activity Levels ($l \in \{0,1,2,3\}$)	Table A6-7/ Figure A7-8
Separation rates for stable partnerships (per partnership-year)	Age ([10-14], …, [50+]yrs); Sexual Activity Levels ($l \in \{0,1,2,3\}$)	Table A8/ Figure A9
Proportion of individuals in stable partnerships	Age (10, …, 19, [20-24], …, [50+]yrs); Sexual Activity Levels ($l \in \{0,1,2,3\}$)	Table A10/ Figure A11
Proportion of partnerships that lead to stable partnerships	Age ([10-14], [15+]yrs); Sexual Activity Levels ($l \in \{0,1,2,3\}$)	Table A9/ Figure A10
Contact rates in stable partnerships (per week)	None	Figure A12
Number of contacts equivalent to casual partnership	None	Figure A13
Onset of sexual activity	Age (10, …, 19yrs); Sexual Activity Levels ($l \in \{0,1,2,3\}$)	Table A11/ Figure A14
Assortative degree for sexual activity matrix	none	Figure A15

	Age matrix, probabilities of one age group to form a partnership with any other age group	Age ([10-14], …, [65+]yrs); Sexual Activity Levels ($l \in \{0,1,2,3\}$); Gender ($g \in \{1,2\}$)	Table A12-14
Natural history (Section 2.2.3)			
	Transmission probability for HPV-16 (per act)	Gender ($g \in \{1,2\}$)	Table A15/ Figure A16
	Relative rate of transmission (vs HPV-16)	HPV-18,6,11,HRC[¥],HRNC[§]	Table A15/ Figure A16
	Clearance rate of infection with HPV-16 (per person-year)	Age ([15-65]yrs[‡]); Gender ($g \in \{1,2\}$)	Table A16/ Figure A17
	Relative rate of clearance from infection (vs HPV-16)	HPV-18,6,11,HRC[¥],HRNC[§]	Table A16/ Figure A18
	Probability of developing lifelong natural immunity	Gender ($g \in \{1,2\}$)	Figure A19
	Progression rates from infection with HPV-16 to CIN1 (per person-year)	None	Table A17/ Figure A21
	Relative rate of progression from infection to CIN1 (vs HPV-16)	HPV-18,6/11[*],HRC[¥],HRNC[§]	Table A17/ Figure A21
	Progression rates from CIN1 with HPV-16 to CIN2 (per person-year)	None	Table A17/ Figure A23
	Relative rate of progression from CIN1 to CIN2 (vs HPV-16)	HPV-18,HRC[¥],HRNC[§]	Table A17/ Figure A23
	Progression rates from CIN2 with HPV-16 to CIN3 (per person-year)	None	Table A17/ Figure A26
	Relative rate of progression from CIN2 to CIN3 (vs HPV-16)	HPV-18,HRC[¥],HRNC[§]	Table A17/ Figure A26
	Progression rate CIN3 to SCC (per person-year)	None	Table A17/ Figure A28
	Regression rate from CIN1 with HPV-16 (per person-year)	None	Table A17/ Figure A22
	Relative rate of regression from CIN1 (vs HPV-16)	HPV-18,6/11[*],HR[#]	Table A17/ Figure A22

	Proportion of regressing CIN1 that clears the infection	None	Table A17/ Figure A20
	Regression rate from CIN2 with HPV-16 to CIN1 (per person-year)	None	Table A17/ Figure A24
	Relative rate of regression from CIN2 to CIN1 (vs HPV-16)	HPV-18,HR[#]	Table A17/ Figure A24
	Regression rate from CIN3 to CIN2 (per person-year)	None	Table A17/ Figure A27
	Clearance rates from CIN2 with HPV-16 (per person-year)	None	Table A17/ Figure A25
	Relative clearance rate from CIN2 (vs HPV-16)	HPV-18,HR[#]	Table A17/ Figure A25
	Progression rate from SCCI to SCCII (per person-year)	None	Table A18
	Progression rate from SCCII to SCCIII (per person-year)	None	Table A18
	Probability of developing symptoms	Stage of SCC	Table A18
	Mortality rates from SCC (per person-year)	Stage of SCC	Table A18
	Progression from infection to other HPV related cancers (cervical adenocarcinoma, cancer of the anus, oropharynx, vulva, vagina and penis)	HPV-16,18,31,33,45,52,58 Gender ($g \in \{1,2\}$)	Table A19/ Figure A29
Screening (Section 2.2.4)			
	Proportion of individuals in screening behaviour levels	Screening Behaviour Levels ($S \in \{0,1,2,3,4\}$)	Table A20
	Age distribution of first screening test	Age (a = [18], …, [38], [39+]yrs)	Figure A30
	Screening rates (per person-year)	Age ([10-14], …,[45-49], [50-59], [60-69], [70+]yrs); Screening behaviour levels ($S \in \{0,1,2,3,4\}$); Previous screening results	Table A21

	Probability of detecting cervical lesions by screening	Severity of lesion (Normal, CIN1, CIN2/3, SCC)	Table A22
	Proportion of individuals followed-up with repeat cytology after an abnormal cytology	Cytology result (ASC-US, LSIL, HSIL)	Table A24
	Proportion of individuals followed-up with colposcopy/biopsy after an abnormal cytology	Cytology result (ASC-US, LSIL, HSIL)	Table A24
	Proportion of individuals lost to follow-up after an abnormal cytology	Cytology result (ASC-US, LSIL, HSIL)	Table A24
	Probability of diagnosing cervical lesions by colposcopy/biopsy	Severity of lesion (Normal, CIN1, CIN2, CIN3, SCC)	Table A23
	Probability of CIN treatment success	None	Section 2.2.4
	Probability of clearing the infection after CIN treatment success	None	Section 2.2.4

¶ Stationary population; ¥ HRC=HR cross-protective : 31, 33, 45, 52, 58; § HRNC=HR non cross-protective : 35, 39, 51, 56, 59, 66, 68, 73, 82; ǂ Linear trend based on values sampled at 15 and 65 years old; *HPV-6 and 11 are modeled separately but have the same value for this parameter; # HR=All high oncogenic risk types

2.2.1 Demographic parameters

Table A3. Mortality rates (per 100,000 person-years) – parameter values[8]

Age group	Female	Male
10-14	13	20
15-19	30	69
20-24	32	80
25-29	33	79
30-34	46	94
35-39	75	126
40-44	114	183
45-49	179	280
50-54	269	435
55-59	430	691
60-64	686	1152
65-69	1138	1896
70-74	1846	3115
75-79	3112	4933
80-84	5341	7890
85-89	9317	12665
90+	17418	20143

Table A4. Hysterectomies unrelated to cervical cancer (per 1000 woman-years) – parameter values[34]

Age group	
0-19	0
20-44	3
45-54	6.5
55-64	3.3
65-130	2.5

2.2.2 Sexual Behavior Parameters

Prior ranges for the sexual behavior parameters are primarily based on data from PISCES (Psychosocial Impact of cervical Screening and Condylomas: an Epidemiological Study)[28,29]. PISCES is a Canadian prospective multicentre clinical study which includes two cohorts: 1) men and women seeking medical care for genital warts and 2) women receiving a normal or an abnormal Pap test result. Recruitment occurred between 2006 and 2008 across Canada. Patients were recruited by general practitioners and gynecologists during the course of routine clinical practice (42 and 59 physicians recruited for the genital warts and Pap test cohorts, respectively). A total of 127 men with genital warts, 145 women with genital warts, 460 women with a normal Pap test results and 492 women with an abnormal Pap test result were recruited in the study[28,29].

Proportion of individuals in sexual activity levels Φ_l. The prior ranges for the proportion of individuals in the different sexual activity levels in Table A5 were calculated from PISCES data. We assumed that individuals in sexual activity levels $l \in \{0, 1, 2, 3\}$ have 0-2, 2-10, 11-39 and 40+ lifetime partners, respectively. The proportions of individuals in each level of sexual activity were calculated using data from the normal and abnormal Pap cohorts, which represent our low (minimum) and high (maximum) sexual activity scenarios, respectively. To be as inclusive as possible, the prior ranges for the proportion of individuals in the sexual activity levels were calculated by multiplying the minimum (maximum) values estimated from PISCES by 80% (120%). Finally, we assume that men have the same priors for the proportion of individuals in the sexual activity levels as women. However, as described later, for a same level of sexual activity men have a higher rate of partner acquisition.

Table A5. Proportion of individuals in the sexual activity levels (Φ_l) - Prior ranges

	$l = 0$		$l = 1$		$l = 2$		$l = 3$	
	Min	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**
Female	0.16	0.36	0.41	0.67	0.14	0.27	0.01	0.02
Male	0.16	0.36	0.41	0.67	0.14	0.27	0.01	0.02

Based on the prior ranges from Table A5, the sampling algorithm proceeds as follows: 1) for each sexual activity level we sample a pseudo-random number and compute a proportion of individuals ($MIN + RAND \cdot (MAX - MIN)$), and 2) we rescale the 4 proportions to ensure they sum to 1. Figure A5 represents the posterior parameter sets for the proportion of individuals in the sexual activity levels.

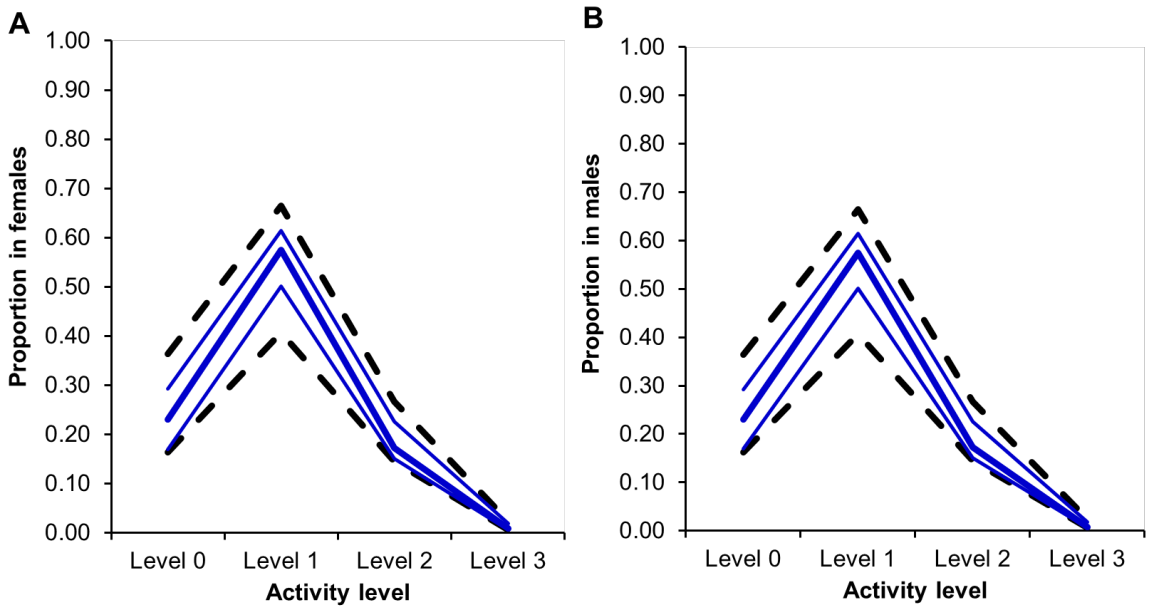


Figure A5. Sexual activity level distribution in A) females and B) males - Posterior distributions. Blue lines represent the median, minimum, and maximum values of the posterior parameter sets. Dashed black lines represent the minimum and maximum values of the prior ranges.

Partner acquisition rates $\theta_{g,l}(a)$. The rate of partner acquisition is the rate of new sexual partner acquisition amongst individuals who are sexually active (i.e. number of new partners per year). The prior ranges for the partner acquisition rates for women by sexual activity level and age were calculated from the PISCES data (all cohorts were included in the analyses). The question analyzed was "How many new sexual partners have you had in the past year". Answers were categorical (0, 1-2, 2-4, 4-10, 11+ partners). Those with more than 10 partners were asked to report the exact number. When calculating the minimum (maximum) scenario we assumed that individuals who reported having 1-2, 2-4 and 4-10 new partners in the last year had 1, 2 and 5 (2,4 and 8) partners, respectively. We assumed that individuals in sexual activity levels $l \in \{0, 1, 2, 3\}$ were those who had 0-2, 2-10, 11-39 and 40+ lifetime partners, respectively. Given that the number of women in some age and level of sexual activity categories were very small, we estimated the rate of partner acquisition by fitting the stratified data using a Gamma function (see Figure A6 for an illustrative example using age-specific minimum data for $l = 0$). The prior ranges for the partner acquisition rates in females were calculated by multiplying the minimum (maximum) values modeled from PISCES by 80% (120%). See Table A6 for the prior ranges of the female partner acquisition rates.

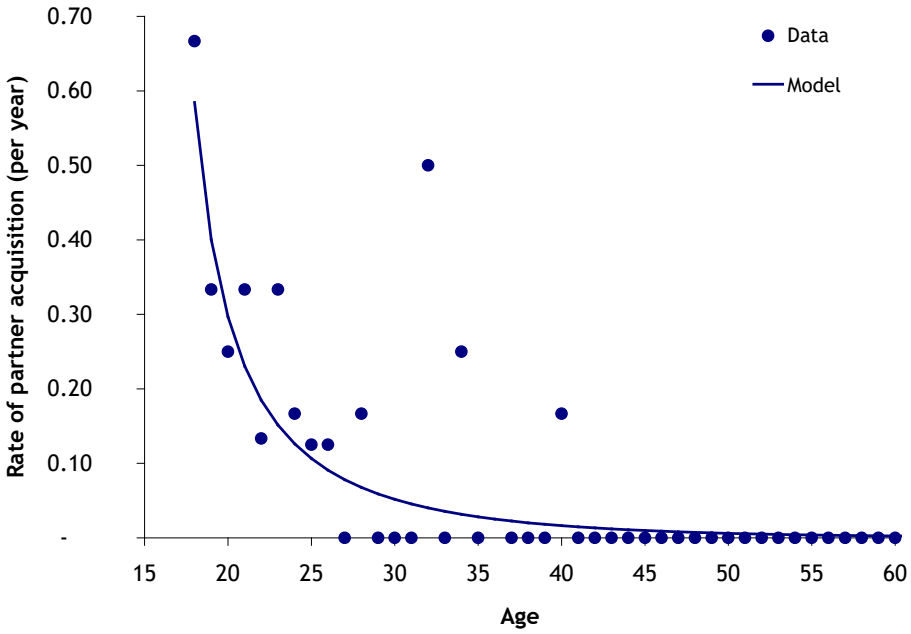


Figure A6. Model fit to age-specific new partner acquisition rates amongst individuals with low sexual activity levels ($l = 0$). Data were taken from PISCES and the model is a Gamma function.

Given that the data available within PISCES for males was limited, we estimated male rates of partner acquisition by multiplying the minimum and maximum female rates (reported in Table A6) by the male to female relative rate (ratio) extracted from two other Canadian studies[35,36]. We did not use the data from Brisson et al.[36] directly to estimate rates of partner acquisition as they were unavailable stratified by our definitions of levels of sexual activity. Refer to Table A7 for the prior ranges for the male partner acquisition rates.

Table A6. Partner acquisition rates for females (per person-year)[§] ($\theta_{g=1,l}(a)$) – Prior ranges

Age groups	$l=0$		$l=1$		$l=2$		$l=3$	
(years)	Min	Max	Min	Max	Min	Max	Min	Max
10-19	0.44	1.05	0.74	1.78	2.04	4.31	4.29	8.74
20-24	0.15	0.64	0.54	1.38	1.52	3.44	4.90	7.76
25-29	0.07	0.46	0.40	1.07	1.11	2.61	2.92	4.73
30-34	0.03	0.34	0.30	0.83	0.80	1.91	1.46	2.64
35-39	0.02	0.26	0.23	0.64	0.56	1.36	0.67	1.41
40-44	0.01	0.20	0.18	0.50	0.39	0.94	0.29	0.73
45-49	0.01	0.15	0.14	0.39	0.27	0.63	0.12	0.38
50-59	0.00	0.12	0.11	0.30	0.19	0.42	0.05	0.19
60-69	0.00	0.06	0.05	0.15	0.09	0.21	0.03	0.10
70+	0.00	0.03	0.03	0.08	0.05	0.10	0.01	0.05

§ Rate among sexually active only.

Table A7. Partner acquisition rates for males (per person-year)[§] ($\theta_{g=2,l}(a)$) - Prior ranges.

Age groups	$l=0$		$l=1$		$l=2$		$l=3$	
(years)	Min	Max	Min	Max	Min	Max	Min	Max
10-19	0.53	1.73	0.90	2.94	2.47	7.12	5.21	14.41
20-24	0.19	0.97	0.68	2.09	1.93	5.21	6.24	11.75
25-29	0.08	0.70	0.48	1.63	1.33	4.00	3.50	7.23
30-34	0.04	0.55	0.35	1.35	0.93	3.12	1.70	4.30
35-39	0.02	0.44	0.27	1.11	0.66	2.34	0.79	2.43
40-44	0.01	0.32	0.21	0.81	0.46	1.53	0.35	1.20
45-49	0.00	0.18	0.10	0.45	0.19	0.74	0.09	0.44
50-59	0.00	0.14	0.08	0.35	0.15	0.49	0.04	0.22
60-69	0.00	0.07	0.04	0.18	0.07	0.24	0.02	0.11
70+	0.00	0.04	0.02	0.09	0.04	0.12	0.01	0.06

§ Rate among sexually active only

From the priors of Table A6 and Table A7, the program samples different partner acquisition rates for each prior parameter set. To allow for realistic trends over age meanwhile keeping the number of varying model parameters to a minimum, the sampling algorithm proceeds as follows. First, because observed data only provides one estimate of partner acquisition for age range 10 to 19 years old, whereas we can expect this rate to vary significantly over this period and early partner acquisition rates (just after the onset of sexual activity) are likely to have an important impact on vaccination strategies, the sampling algorithm allows the partner acquisition rates (among those sexually active) to

follow an increasing linear trend from 10 to 19 years of age. This is done by sampling one rate for 10-year-olds (start) and one rate for 19-year-olds. Because we assume the rates are increasing, the start rates are sampled between 0 and the upper limits of the prior ranges defined in Table A6 and Table A7, and the 19-year-old rates are sampled between the start rates and the upper limits of the prior ranges. Second, to minimize the number of dimensions of the Latin Hypercube, we sample one random number per sexual activity level that we call relative rate (RR_l), and compute the rates over age with the formula:

$$\theta_{g,l}(a) = \min(g,a,l) + RR_l \cdot \left[\max(g,a,l) - \min(g,a,l)\right] \quad (2.1)$$

Where a is the age group, and min and max are the minimum and maximum of the age and sexual activity level specific prior ranges, respectively. Figure A7 and A8 represent the posterior parameters sets for the female and male rates of partner acquisition, respectively.

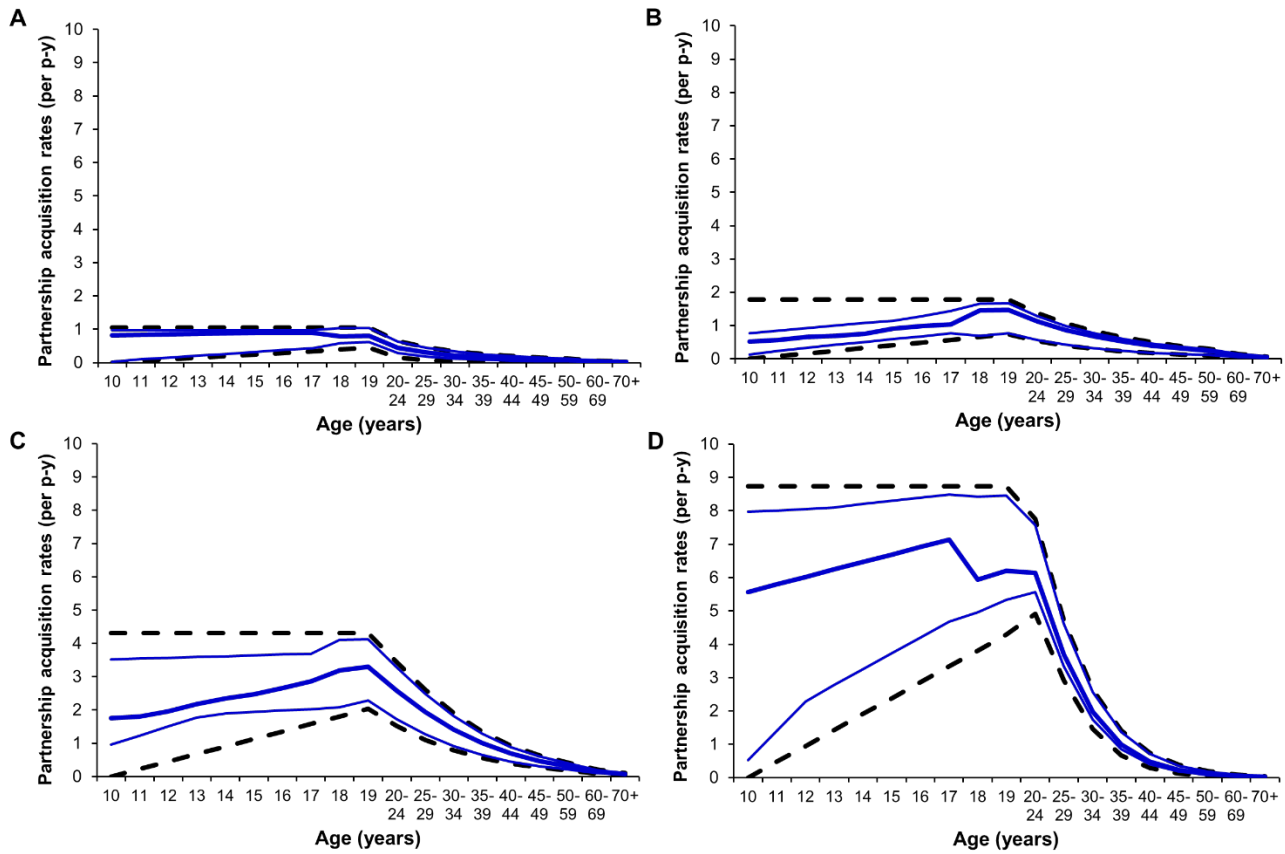


Figure A7. Partner acquisition rates of sexually active females in sexual activity level A) $l = 0$, B) $l = 1$, C) $l = 2$ and D) $l = 3$ - Posterior distributions. Dashed black lines represent the minimum and maximum values of the prior ranges over age. Blue lines represent the median, minimum, and maximum values of the posterior parameter sets.

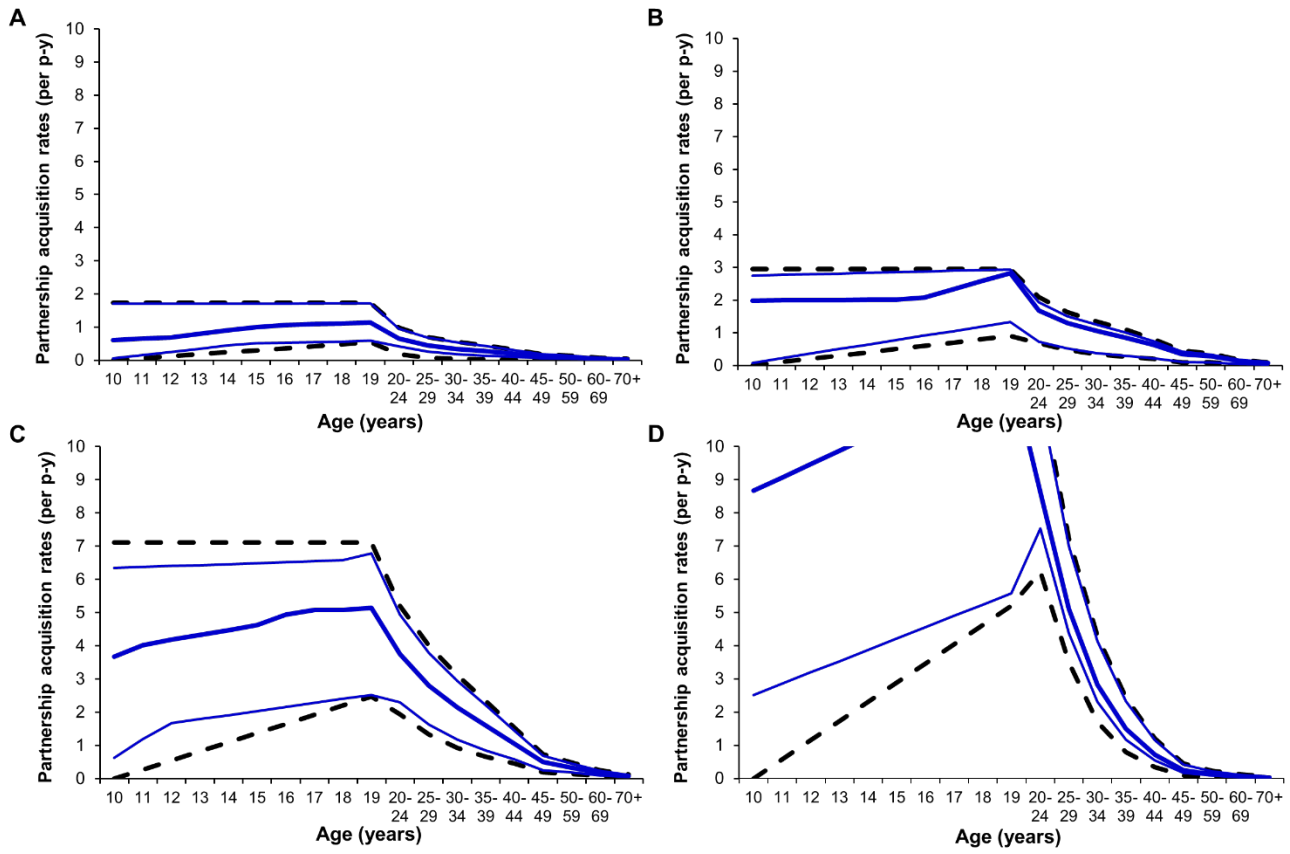


Figure A8. Partner acquisition rates of sexually active males in sexual activity level A) $l = 0$, B) $l = 1$, C) $l = 2$ and D) $l = 3$ - Posterior distributions. Dashed black lines represent the minimum and maximum values of the prior ranges over age. Blue lines represent the median, minimum, and maximum values of the posterior parameter sets.

Stable partnership separation rates $\sigma_l(a)$. The rate of separation amongst stable partnerships $\sigma_l(a)$ was estimated from two sources. The maximum scenario for stable partnership separation rates were calculated from PISCES data (all female cohorts were included in the analyses). We assumed that the rate of separation, stratified by age and level of sexual activity, was equal to 1/average duration of partnerships $d_l(a)$. Since the average duration of a partnership in PISCES is right censored, we most likely overestimate the rate of separation. The minimum rates of separation were derived from Canadian divorce rates[37]. Given the uncertainty around our estimates of separation rates, the prior ranges were calculated by multiplying the minimum and maximum estimated values by 80% and 120% (see Table A8 for priors). The program used Equation (2.1) to sample the separation rates from prior ranges (see Figure A9 for the posterior separation rates). Partnership separation can also occur following the death of one of the stable partners.

Table A8. Stable partnership separation rates (per partnership-year) $\sigma_l(a)$ – Prior ranges

Age (yrs)	$l = 0$		$l = 1$		$l = 2$		$l = 3$	
	Min	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**
10-14	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
15-19	0.10	0.74	0.12	0.88	0.14	1.04	0.32	2.40
20-24	0.05	0.34	0.08	0.61	0.11	0.85	0.26	2.00
25-29	0.03	0.21	0.05	0.34	0.06	0.43	0.13	1.02
30-34	0.02	0.13	0.03	0.20	0.04	0.27	0.09	0.69
35-39	0.01	0.08	0.02	0.13	0.06	0.44	0.16	1.20
40-44	0.01	0.07	0.01	0.09	0.02	0.14	0.03	0.24
45-49	0.01	0.05	0.01	0.09	0.01	0.10	0.01	0.10
50-59	0.00	0.04	0.01	0.08	0.01	0.07	0.01	0.10
60-69	0.00	0.02	0.00	0.03	0.00	0.03	0.01	0.04
70+	0.00	0.01	0.00	0.01	0.00	0.01	0.00	0.02

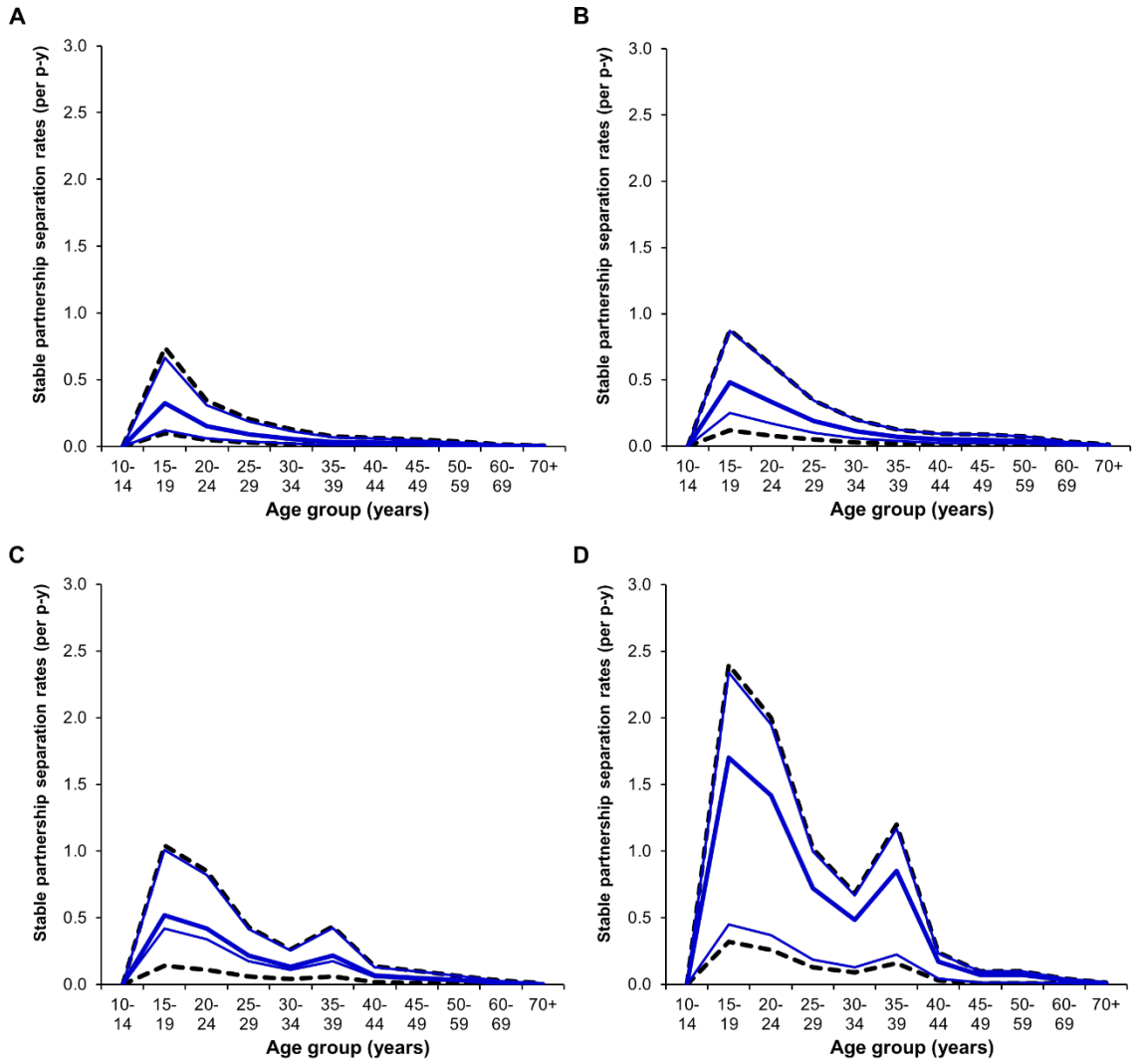


Figure A9. Stable partnership separation rates by level of sexual activity A) $l = 0$, B) $l = 1$, C) $l = 2$ and D) $l = 3$ - Posterior distributions. Dashed black lines represent the minimum and maximum values of the prior ranges over age. Blue lines represent the median, minimum, and maximum values of the posterior parameter sets.

Proportion of women in a stable partnership $\Psi_l(a)$. The prior ranges for the proportion of women in a stable relationship by age and level of sexual activity $\Psi_l(a)$ were calculated from PISCES and the Canadian Community Health Survey (CCHS), Cycle 3.1[38]. From PISCES, we estimated the proportion of sexually active women in stable relationships. The question analyzed was "Are you in a stable relationship". We assumed that individuals in sexual activity levels $l \in \{0, 1, 2, 3\}$ were those who had 0-2, 2-10, 11-

39 and 40+ lifetime partners, respectively. The normal and abnormal Pap cohorts were used to calculate the minimum and maximum bounds, respectively. To estimate the age and level of sexual activity specific proportion of women in a stable relationship $\Psi_l(a)$ we multiplied the proportion of sexually active women in a stable relationship by the proportion of women sexually active. The proportion of women that are sexually active by age and level of sexual activity were estimated from the CCHS. The prior ranges were calculated by multiplying the minimum (maximum) values by 80% (120%) (see Table A9 for priors). The program used Equation (2.1) to sample the proportions of women in stable partnerships from prior ranges. Figure A10 shows the posterior proportions of women in stable partnerships.

Table A9. Proportions of women in stable partnerships§ ($\Psi_l(a)$) - Prior ranges

Age groups	$l=0$		$l=1$		$l=2$		$l=3$	
(years)	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**
15	4%	12%	10%	30%	17%	54%	17%	52%
16	8%	20%	22%	52%	28%	68%	28%	65%
17	16%	36%	29%	65%	32%	74%	32%	71%
18	25%	52%	39%	79%	37%	79%	37%	76%
19	33%	61%	46%	83%	41%	79%	41%	76%
20-24	44%	70%	54%	85%	48%	81%	48%	77%
25-29	66%	99%	62%	97%	58%	88%	51%	80%
30-39	72%	100%	69%	100%	63%	98%	53%	90%
40-49	73%	100%	69%	100%	58%	96%	60%	90%
50-59	71%	100%	70%	100%	67%	100%	60%	90%
60-69	71%	100%	70%	100%	67%	100%	60%	90%
70+	71%	100%	70%	100%	67%	100%	60%	90%

§ Women 60+ years old were given the same priors as those aged 50-59 years.

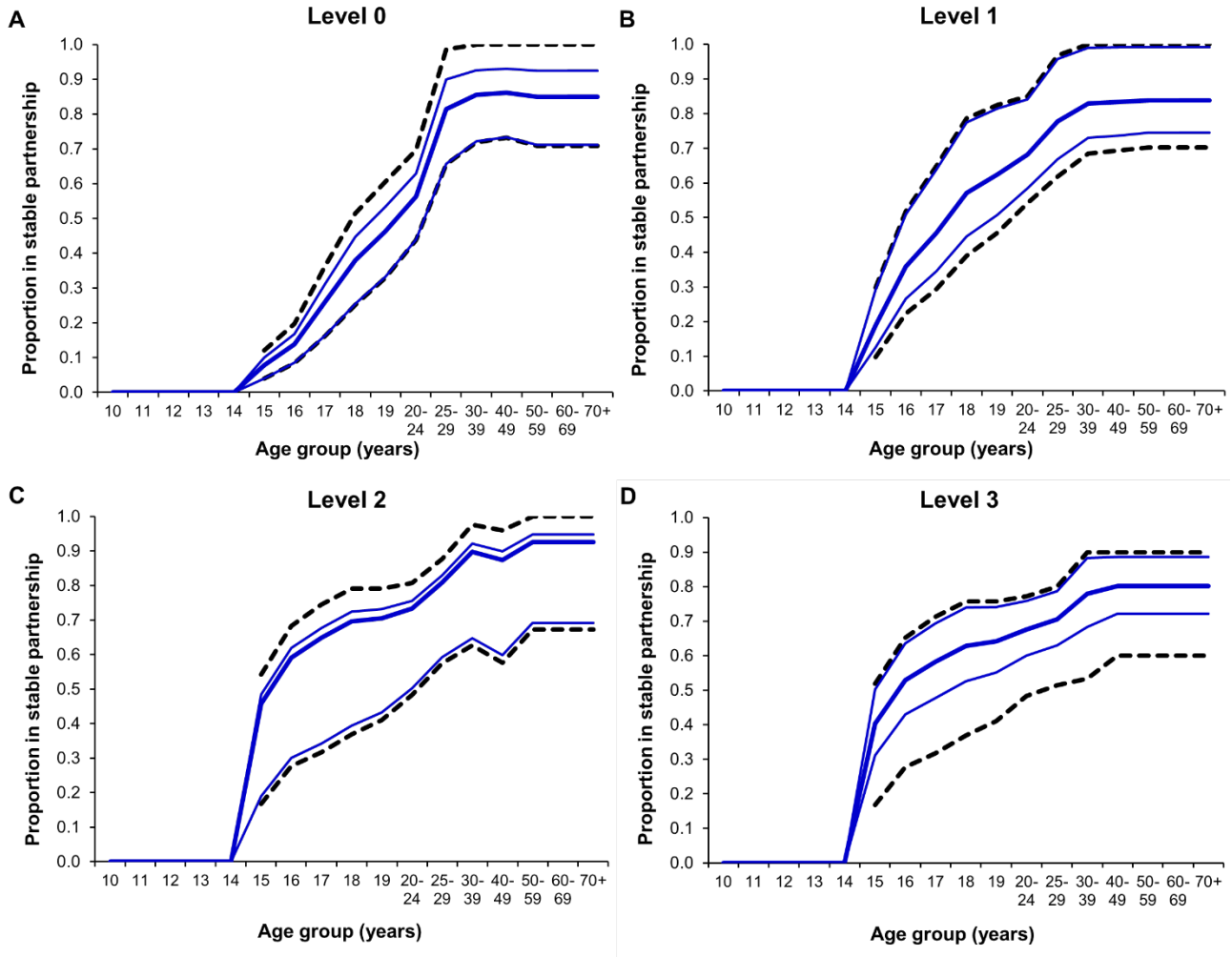


Figure A10. Proportions of women in stable partnerships by age and level of sexual activity A) $l = 0$, B) $l = 1$, C) $l = 2$ and D) $l = 3$ - Posterior distributions. Dashed black lines represent the minimum and maximum values of the prior ranges over age. Blue lines represent the median, minimum, and maximum values of the posterior parameter sets.

Proportion of new partnerships that lead to stable partnerships $\psi_l(a)$. The prior ranges for the proportion of new partnerships that lead to stable partnerships by sexual activity levels and age were calculated using the following formula:

$$\psi_l(a) = \begin{pmatrix} \text{\% new} \\ \text{partnerships} \\ \text{that lead to a} \\ \text{stable} \\ \text{partnership} \end{pmatrix} = \frac{\begin{pmatrix} \text{\% in stable} \\ \text{relationship} \end{pmatrix} \times \begin{pmatrix} \text{Rate of} \\ \text{separation} \end{pmatrix}}{\left(1 - \begin{pmatrix} \text{\% in stable} \\ \text{relationship} \end{pmatrix}\right) \times \begin{pmatrix} \text{Rate of partner} \\ \text{acquisition singles} \end{pmatrix}}$$

or:

$$\psi_l(a) = \frac{\Psi_l(a) \cdot \sigma_l(a)}{\left[1 - \Psi_l(a)\right] \cdot \varsigma_l(a)}. \tag{2.2}$$

The age and level of sexual activity specific proportion of individuals in a stable relationship, rate of partnership separation amongst stable relationships and rate of partner acquisition amongst singles were all estimated from PISCES data. We assumed that individuals in sexual activity levels $l \in \{0, 1, 2, 3\}$ were those who had 0-2, 2-10, 11-39 and 40+ lifetime partners, respectively. For women aged 15+ and in levels of sexual activity $l \in \{0, 1, 2, 3\}$, the estimated proportions of partnerships that lead to stable partnerships varied between 0.81-1.00, 0.25-0.65, 0.09-0.51 and 0.08-0.17, respectively. We assumed that all relationships involving 10-14 year olds are casual (i.e., do not lead to stable relationships). See Table A10 for prior ranges. From the Latin Hypercube, 4 random numbers are attributed to each prior parameter set and the sampling algorithm computes the level of sexual activity specific proportions of new partnerships that lead to stable partnership using Equation (2.1). Figure A11 shows the posterior distributions for the proportions of new partnerships that lead to stable partnership.

Table A10. Proportion of new partnerships that lead to a stable partnership $\Psi_l(a)$ – Prior ranges

	$l = 0$		$l = 1$		$l = 2$		$l = 3$	
	Min	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**
10-14 YRS	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
15+ YRS	0.81	1.00	0.25	0.65	0.09	0.51	0.08	0.17

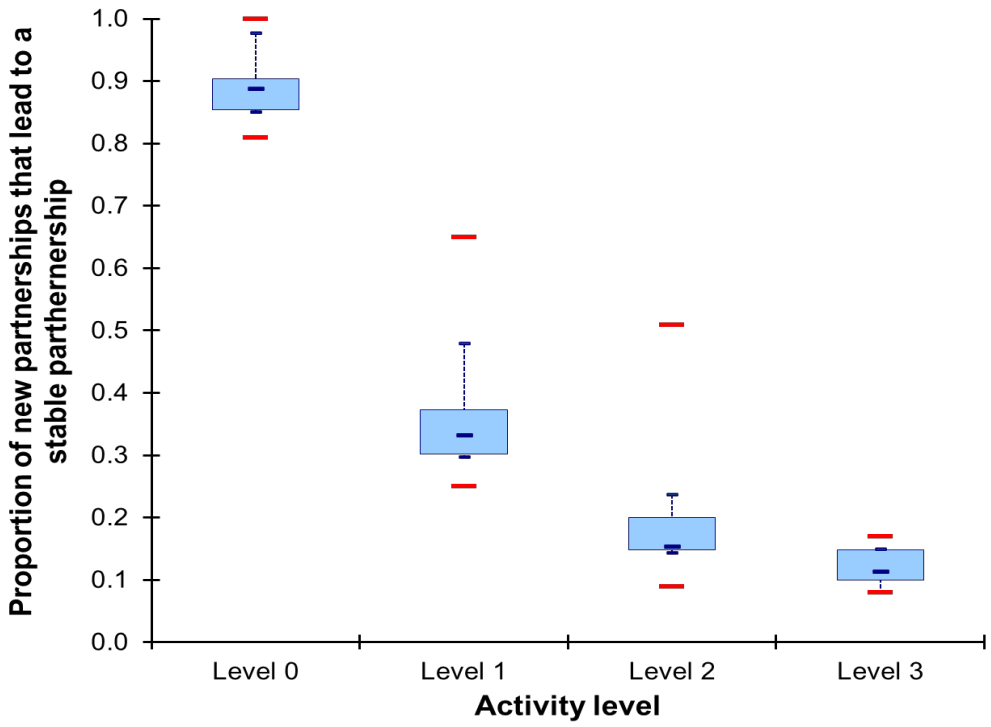


Figure A11. Proportions of new partnerships that lead to a stable partnership - Posterior distributions. Box plots represent the medians, and 10, 25, 75, and 90th percentiles of the posterior parameter sets. Red lines represent the minimum and maximum values of the prior ranges.

Frequency of sex acts in stable partnerships ω. During the course of a stable partnership, the average frequency of sex acts is assumed to vary between 1.5 and 4 acts per week[39-41]. The frequency of sex acts during a stable partnership ω is assumed to be independent of the age and level of sexual activity of the partners, and the duration of the partnership. However, the duration of a partnership is dependent on the age and level of sexual activity of the partners (see Stable partnership separation rates). From the Latin Hypercube, 1 random number is attributed to each prior parameter set by the sampling algorithm and the weekly frequency of sex acts in a stable relationship is computed using Equation (2.1). Figure A12 represents the posterior distribution for the weekly frequency of sex acts in a stable relationship.

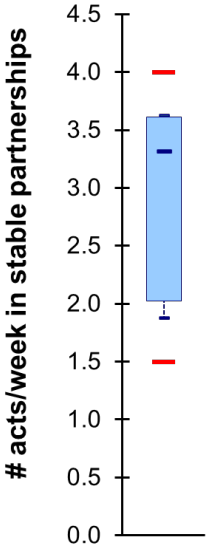


Figure A12. Number of acts per week in stable partnerships - Posterior distributions. Box plots represent the medians, and 10, 25, 75, and 90th percentiles of the posterior parameter sets. Red lines represent the minimum and maximum values of the prior range.

Number of sex acts per casual partnership C. We set the prior range for the average number of sex acts per casual partnership C to between 1.5 and 4.0. Casual partnerships are assumed to be instantaneous (see Figure A1, Section 1.2.2). It should be noted that the number of sex acts during a casual partnership is independent of the age and level of sexual activity of the partners. From the Latin Hypercube, 1 random number is attributed to each prior parameter set by the sampling algorithm and the number of sex acts per casual partnership is computed using Equation (2.1). Figure A13 represents the posterior distribution for the number of sex acts per casual partnership.

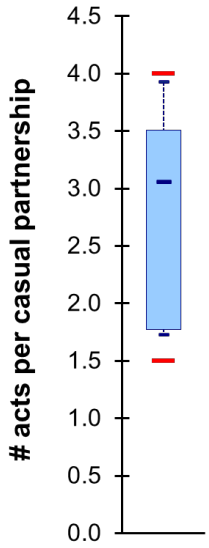


Figure A13. Number of acts per casual partnership - Posterior distributions. Box plots represent the medians, and 10, 25, 75, and 90th percentiles of the posterior parameter sets. Red lines represent the minimum and maximum values of the prior range.

Onset of sexual activity in females $\varphi(a)$.In the model, it was impossible to fit the onset of sexual activity in girls using the age-specific rates of partner acquisition (amongst sexually active women) because the age-specific rate towards the first sexual partnership is different to subsequent partnerships. To define the prior ranges for the rates of onset of sexual activity, we first computed the exact rates required to fit the CCHS data on the percentage of girls who ever had sex (stratified by age and level of sexual activity)[38], then we allowed for a 20% variation above and under these estimates. The sampling algorithm provides each prior parameter set with rates of onset of sexual activity computed using Equation (2.1) and 4 random numbers from the Latin Hypercube (1 per level of sexual activity). Refer to Table A11 for prior ranges and to Figure A14 for the posterior distributions of the rates of onset of sexual activity in girls/women.

Table A11. Rates of onset of sexual activity for girls $\varphi(a)$ – Prior ranges

Age	$l=0$		$l=1$		$l=2$		$l=3$	
(years)	Min	Max	Min	Max	Min	Max	Min	Max
10	0.000	0.000	0.003	0.004	0.011	0.017	0.011	0.017
11	0.000	0.000	0.009	0.013	0.022	0.032	0.022	0.032
12	0.000	0.000	0.009	0.013	0.022	0.032	0.022	0.032
13	0.000	0.000	0.033	0.049	0.129	0.194	0.129	0.194
14	0.020	0.029	0.033	0.049	0.129	0.194	0.129	0.194
15	0.057	0.086	0.157	0.235	0.129	0.194	0.129	0.194
16	0.064	0.096	0.214	0.321	0.202	0.303	0.202	0.303
17	0.160	0.240	0.214	0.321	0.202	0.303	0.202	0.303
18	0.160	0.240	0.326	0.489	0.202	0.303	0.202	0.303
19	0.163	0.244	0.326	0.489	0.257	0.386	0.257	0.386
20-24	0.095	0.143	0.261	0.391	0.271	0.406	0.271	0.406

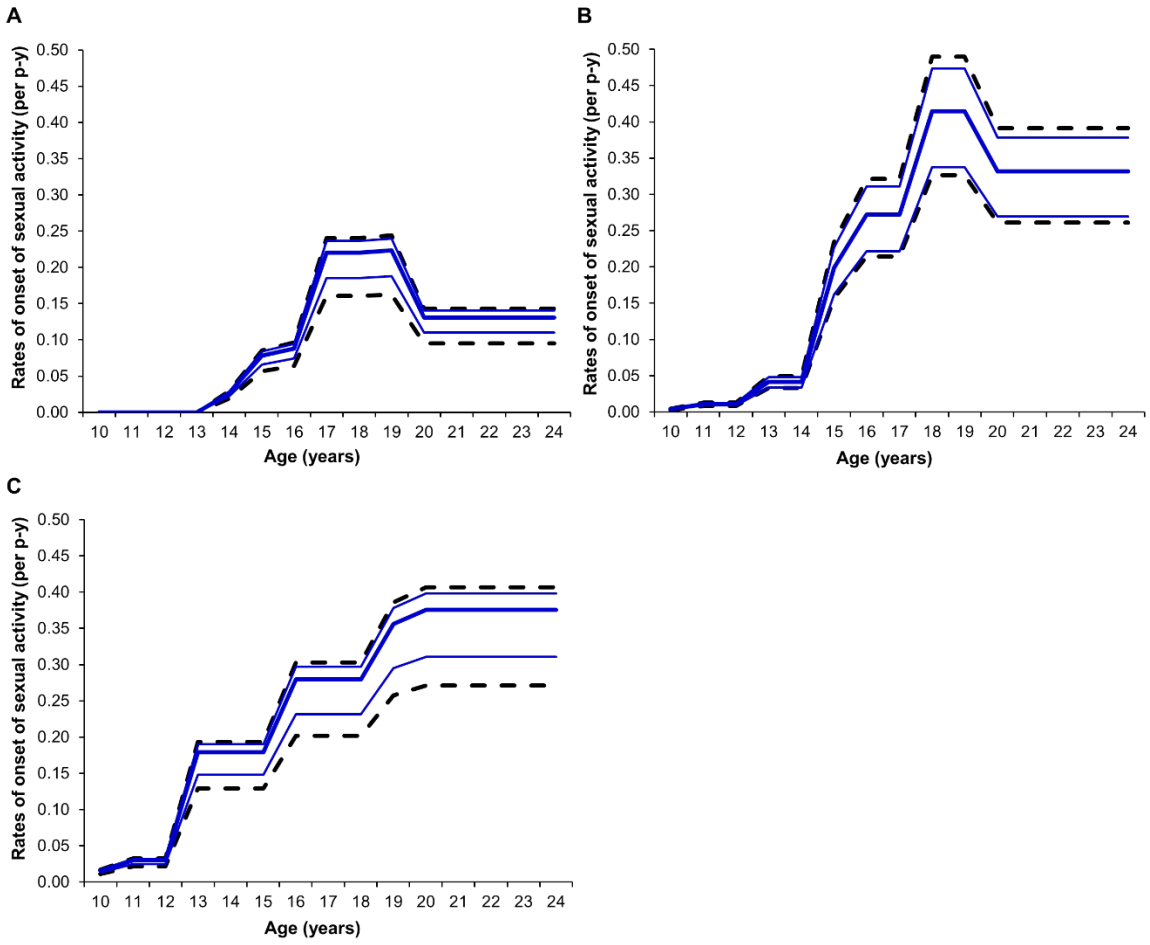


Figure A14. Rate of onset of sexual activity for girls in sexual activity level A) $l = 0$, B) $l = 1$, and C) $l = 2, 3$ - Posterior distributions. Dashed black lines represent the minimum and maximum values of the prior ranges over age. Blue lines represent the median, minimum and maximum values of the posterior parameter sets.

Assortative degree of mixing by level of sexual activity κ. Refer to Section 1.2.3 for the definition of the mixing matrices. In particular, Equation (1.2) and (1.3) define the mixing by level of sexual activity $\Gamma = [\Gamma_{l,l',g}]$ and the assortative degree κ, respectively. For each prior parameter set, 1 assortative degree is sampled from 50 to 150 using a uniform distribution. See Figure A15 for the posterior distribution of the assortative degree.

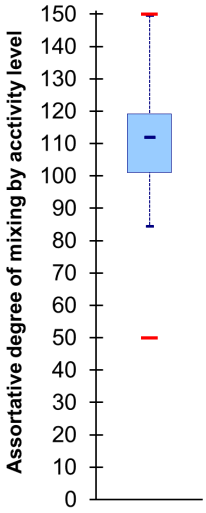


Figure A15. The assortative degree of the mixing by level of sexual activity - Posterior distributions. Box plots represent the medians, and 10, 25, 75, and 90th percentiles of the posterior parameter sets. Red lines represent the minimum and maximum values of the prior range.

Age mixing matrix $\Lambda = [\Lambda_{a,a',l,g}]$. The age mixing matrix was estimated by calculating the age distribution of the male partners of women in PISCES (all cohorts were included in the analyses). The question analyzed was "How old is your most recent sexual partner". We assumed that women in sexual activity levels $l \in \{0, 1, 2, 3\}$ were those who had 0-2, 2-10, 11-39 and 40+ lifetime partners, respectively. Given that the number of women in some age and level of sexual activity categories were very small, we fit the age distribution of males using a Gamma function. See Table A12-A14 for the values of the mixing matrices.

Table A12. Age mixing matrix $\Lambda = [\Lambda_{a,a',l=0,g}]$ – Level of sexual activity $l = 0$

Men\Women Age (years)	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65+
10-14	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
15-19	17%	5%	0%	0%	0%	0%	0%	0%	0%	0%	0%
20-24	82%	62%	14%	0%	0%	0%	0%	0%	0%	0%	0%
25-29	1%	27%	49%	13%	0%	0%	0%	0%	0%	0%	0%
30-34	0%	5%	29%	41%	11%	0%	0%	0%	0%	0%	0%
35-39	0%	1%	7%	29%	40%	11%	0%	0%	0%	0%	0%
40-44	0%	0%	1%	12%	34%	40%	10%	0%	0%	0%	0%
45-49	0%	0%	0%	4%	12%	34%	46%	10%	0%	0%	0%
50-54	0%	0%	0%	1%	2%	12%	37%	46%	11%	0%	0%
55-59	0%	0%	0%	0%	0%	2%	7%	37%	53%	11%	0%
60-64	0%	0%	0%	0%	0%	0%	0%	7%	30%	53%	11%
65+	0%	0%	0%	0%	0%	0%	0%	0%	7%	36%	89%

Table A13. Age mixing matrix $\Lambda = [\Lambda_{a,a',l=1,g}]$ – Level of sexual activity $l = 1$

Men\Women Age (years)	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65+
10-14	1%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
15-19	26%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
20-24	58%	36%	14%	1%	0%	0%	0%	0%	0%	0%	0%
25-29	15%	49%	47%	16%	0%	0%	0%	0%	0%	0%	0%
30-34	1%	12%	28%	38%	8%	0%	0%	0%	0%	0%	0%
35-39	0%	2%	9%	30%	36%	18%	0%	0%	0%	0%	0%
40-44	0%	0%	2%	12%	34%	44%	24%	0%	0%	0%	0%
45-49	0%	0%	0%	3%	16%	23%	55%	24%	0%	0%	0%
50-54	0%	0%	0%	1%	5%	9%	17%	55%	14%	0%	0%
55-59	0%	0%	0%	0%	1%	3%	3%	17%	43%	14%	0%
60-64	0%	0%	0%	0%	0%	1%	0%	3%	26%	43%	14%
65+	0%	0%	0%	0%	0%	0%	0%	1%	17%	43%	86%

Table A14. Age mixing matrix $\Lambda_{a,a',l=\{2,3\},g}$ - Level of sexual activity $l = 2, 3$

Men\Women Age (years)	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65+
10-14	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
15-19	37%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
20-24	50%	37%	14%	0%	0%	0%	0%	0%	0%	0%	0%
25-29	11%	50%	47%	28%	0%	0%	0%	0%	0%	0%	0%
30-34	2%	11%	28%	45%	20%	0%	0%	0%	0%	0%	0%
35-39	0%	2%	9%	18%	39%	20%	0%	0%	0%	0%	0%
40-44	0%	0%	2%	6%	22%	39%	20%	0%	0%	0%	0%
45-49	0%	0%	0%	2%	11%	22%	39%	20%	0%	0%	0%
50-54	0%	0%	0%	1%	5%	11%	22%	39%	20%	0%	0%
55-59	0%	0%	0%	0%	2%	5%	11%	22%	39%	20%	0%
60-64	0%	0%	0%	0%	1%	2%	5%	11%	22%	39%	20%
65+	0%	0%	0%	0%	1%	2%	4%	9%	19%	41%	80%

2.2.3 Biological Parameters

Per-act transmission probability β_g^τ. The transmission probability of HPV infection per act or per partnership has yet to be empirically estimated. The transmission probabilities used in previous modeling studies were mainly per partnership and varied significantly from one study to another[41-44]. The only study which has examined the per-act transmission probability is Burchell et al.[41], which estimated the range to be 5–100%. We use this range for our uniform prior distribution of the per-act transmission probability.

Given the important differences in the prevalence of the different HPV types (and similarities in clearance rates [45]), it is likely that the transmission probability is type-specific. Therefore, in our model, we allocated different per-act transmission probabilities to types HPV-16, 18, 6, 11, cross-protective and non cross-protective high-risk types (HR Cross: 31, 33, 45, 52, 58; HR Not Cross: 35, 39, 51, 56, 59, 66, 68, 73, 82). Furthermore, we allow male-to-female and female-to-male transmission probabilities to be different. Transmission probabilities are sampled as follows:

- A female-to-male ($\mathrm{F} \rightarrow \mathrm{M}$) transmission probability $\beta_{g=2}^{\tau}$ is sampled from the uniform distribution 5-100% and is attributed to HPV-16. The remaining transmission probabilities are relative to the base HPV-16 value.

- An HPV-16 male-to-female ($\mathrm{M} \rightarrow \mathrm{F}$) transmission probability $\beta_{g=1}^{\tau}$ is computed by multiplying the female-to-male value with a relative probability, $RP_{M \rightarrow F}^{\text{HPV-16}}$, sampled from a uniform prior distribution of 0.4-2.00:

$$\beta_{g=1}^{\text{HPV-16}} = \beta_{g=2}^{\text{HPV-16}} \cdot RP_{M \rightarrow F}^{\text{HPV-16}} \tag{2.3}$$

- Finally, we sample relative probabilities (vs. HPV-16) for HPV-18, HPV-6, 11, HR Cross and HR Not Cross types from the prior ranges defined in Table A15. The female-to-male and male-to-female transmission probabilities are then computed by multiplying the respective HPV-16 transmission probabilities ($\mathrm{F} \rightarrow \mathrm{M}$ & $\mathrm{M} \rightarrow \mathrm{F}$) by these relative probabilities RP^{τ}:

$$\beta_{g}^{\tau} = \min\left\{\beta_{g}^{\text{HPV-16}} \cdot RP^{\tau},\ 1\right\} \tag{2.4}$$

Figure A16 shows the posterior per-act transmission probabilities.

Table A15. Transmission probabilities per-act β_g^{τ} – Prior ranges

	MIN	MAX
Per-act probability of HPV-16 transmission (female-to-male) $\beta_{g=2}^{\text{HPV-16}}$	0.05	1.00
Relative Probability HPV-16 male-to-female (vs. $\beta_{g=2}^{\text{HPV-16}}$) $RP_{M\to F}^{\text{HPV-16}}$	0.40	2.00
Relative Probabilities (vs. $\beta_g^{\text{HPV-16}}$)		
$RP^{\text{HPV-18}}$	0.11	1.00
$RP^{\text{HPV-6}}$	0.20	1.00
$RP^{\text{HPV-11}}$	0.13	0.50
RP^{Cross} ¶	0.02	0.72
RP^{NotCross} ¶	0.02	0.72

¶ Cross: high-risk cross-protective types 31, 33, 45, 52, 58; Not Cross: high-risk non cross-protective types 35, 39, 51, 56, 59, 66, 68, 73, 82. Although the cross-protective and non cross-protective types have the same priors, they`ll take different values in all parameter sets.

Given that there is no evidence on the relative transmission probabilities of one HPV-type versus others, assumptions were made to estimate the priors. Relative transmission probabilities of types versus HPV-16 were estimated to equal to the Relative Prevalence of these types. For each type, the prior ranges are the minimum and maximum Relative Prevalence (versus HPV-16) estimated from the Biomarkers of Cervical Cancer Risk Study (BCCR)[1], the McGill/Concordia Cohort (McGill)[2] and the Canadian Cervical Cancer Screening Trial (CCCaST)[6]. Our priors encompass the values from Choi et al., which estimate that the Relative transmission probability of HPV-18, HPV-6 and HPV-OHR versus HPV-16 are 0.38-0.50, 0.25-0.92 and 0.19-0.38[43].

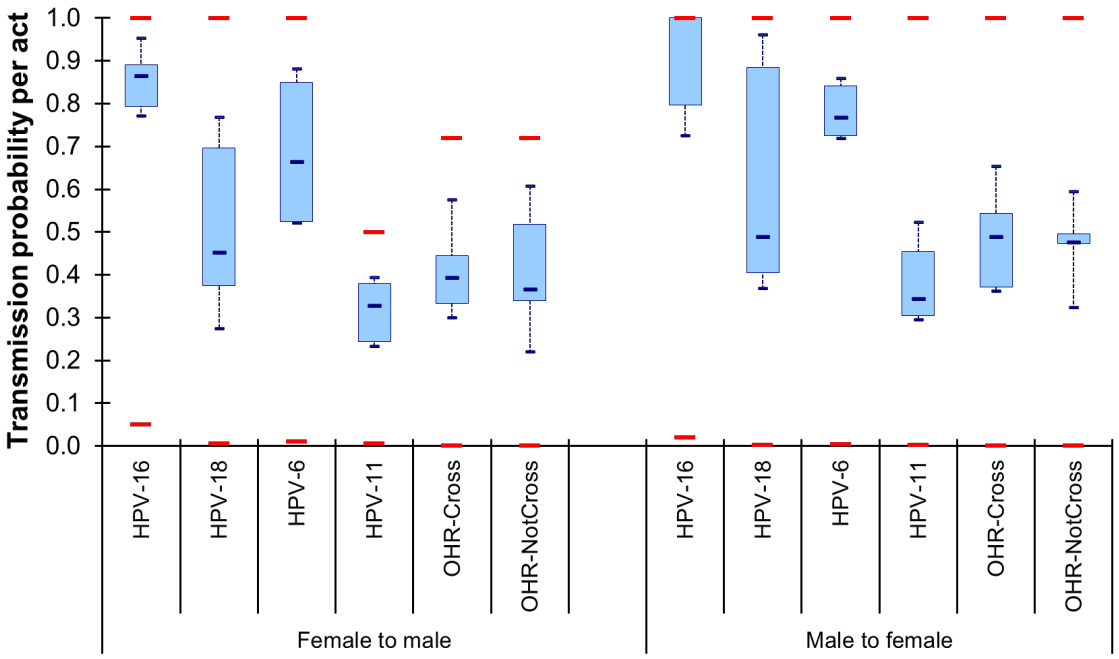


Figure A16. Per-act transmission probabilities - Posterior distributions. Box plots represent the medians, and 10, 25, 75, and 90th percentiles of the posterior parameter sets. Red lines represent the minimum and maximum values of the prior ranges.

Clearance rates $\gamma_g^{\tau}(a)$. Type-specific clearance rates were extracted from Insinga et al.[46], Kulmala et al.[47] and Trottier et al.[45] (see Table A16). It is unknown whether clearance rates are age dependent. To allow clearance to be age dependent whilst keeping the number of parameters to a minimum, we modeled age-specific clearance rates using a linear trend. For female and male clearance rates, we sample two points from the uniform distribution of HPV-16 clearance (Table A16). These values are attributed to the first and last age groups, and clearance rates for the intermediate age groups are inferred from the linear trend joining the two values. The HPV-16 clearance rates serve as reference rates. Relative rates for HPV-18, 6, 11, HR cross-protective and non cross-protective types are sampled from the uniform distributions presented in Table A16. Clearance rates for HPV-18, 6, 11, cross-protective and non cross-protective high-risk types are obtained by multiplying the HPV-16 rates with the sampled relative rates:

$$\gamma_g^{\tau}(a) = \gamma_g^{\text{HPV-16}}(a) \cdot RR^{\tau} \qquad (2.5)$$

We assumed the same parameter priors for HPV-16 clearance rates for men and women based on results published by Giuliano et al. [48]. Of note, the posterior parameter values for the clearance rates are allowed to be different for females and males.

Of note, even though the high risk types labeled as cross-protective have the same clearance rates, it is important to understand that they are modeled individually and not as a group of types. Figure A17 shows the posterior HPV-16 clearance rates for females and males, and Figure A18 shows the posterior distribution of the relative clearance rates compared to HPV-16.

Table A16. HPV clearance rates $\gamma_g^{\tau}(a)$ – Prior ranges

	MIN	MAX
Clearance rate HPV-16 women (per-year)¶ $\gamma_{g=1}^{\text{HPV-16}}(a)$	0.58	1.70
Relative Rate (vs $\gamma_g^{\text{HPV-16}}(a)$)¥		
$RR^{\text{HPV-18}}$	0.93	1.12
$RR^{\text{HPV-6}}$	1.27	1.96
$RR^{\text{HPV-11}}$	1.27	2.17
RR^{Cross} ‡	0.79	1.57
RR^{NotCross} ‡	0.79	1.57
Clearance rate HPV-16 men (per-year) §	0.58	1.70

¶. Minimum and maximum value taken from the minimum and maximum bound of the confidence intervals from [46,47]. ¥. Minimum and Maximum are the minimum and maximum Relative Rates from [1,2,6,45,46]. §. We assumed same range as for women. ‡ Cross: high-risk cross-protective types 31, 33, 45, 52, 58; Not Cross: high-risk non cross-protective types 35, 39, 51, 56, 59, 66, 68, 73, 82.

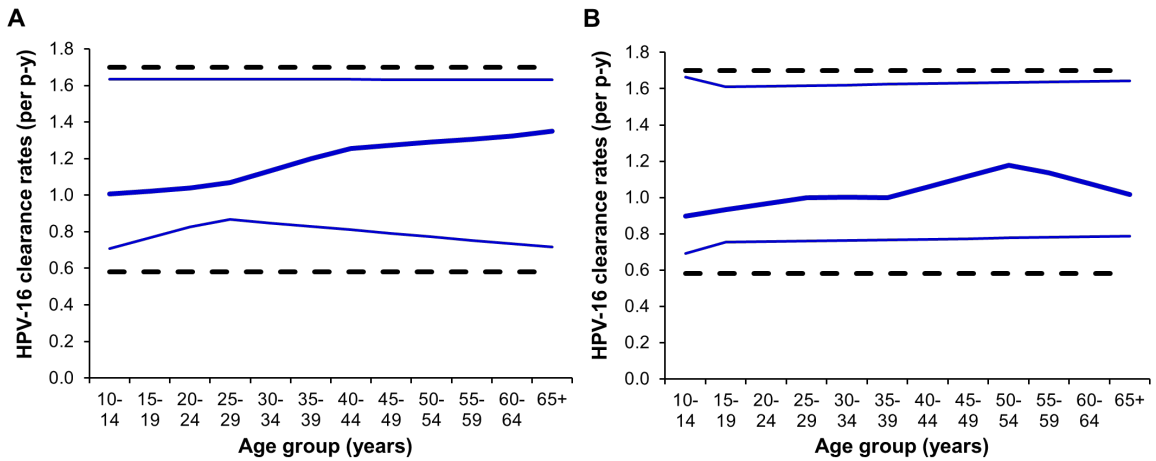


Figure A17. HPV-16 clearance rates for A) females and B) males **- Posterior distributions.** Dashed black lines represent the minimum and maximum values of the prior ranges. Blue lines represent the minimum, median and maximum values of the posterior parameter sets.

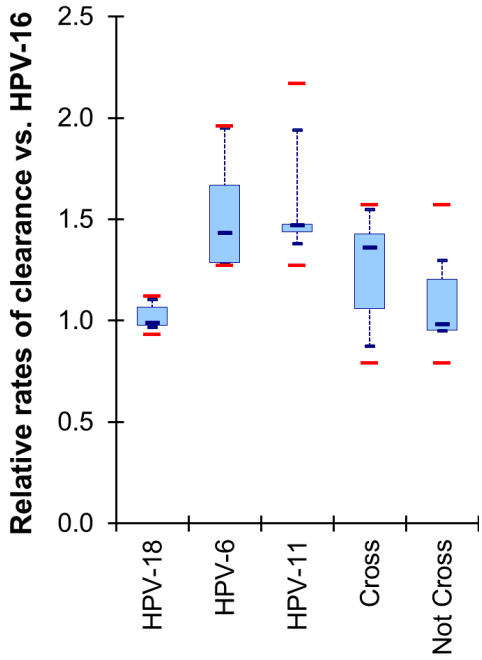


Figure A18. Relative clearance rates compared to HPV-16 - Posterior distributions. Box plots represent the medians, and 10, 25, 75, and 90th percentiles of the posterior parameter sets. Red lines represent the minimum and maximum values of the prior ranges. Cross: high-risk cross-protective types 31, 33, 45, 52, 58; Not Cross: high-risk non cross-protective types 35, 39, 51, 56, 59, 66, 68, 73, 82.

Probability of developing lifelong natural immunity M_g. We use an uninformed prior for the male and female probabilities of developing lifelong natural immunity following clearance of infection (0-100%) given the lack of empirical data in the literature. See Figure A19 for posterior distributions.

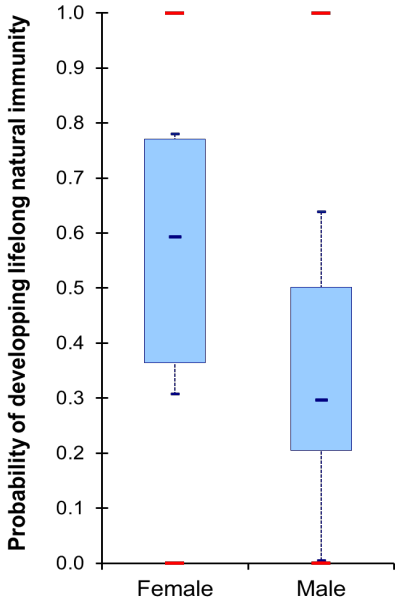


Figure A19. Probabilities of developing lifelong natural immunity following clearance of infection - Posterior distributions. Box plots represent the medians, and 10, 25, 75, and 90th percentiles of the posterior parameter sets. Red lines represent the minimum and maximum values of the prior ranges.

Progression, regression and clearance rates for cervical intraepithelial lesions. Although several epidemiological studies have estimated the probability of developing CIN lesions following an HPV infection, it is very difficult to directly estimate progression and regression rates between the different grades of CIN from these studies. The different study designs, follow-up intervals, performance of screening for the detection of cervical lesions and protocols for the management of abnormal results lead to values that differ widely between studies.

To overcome this difficulty, we developed a simple Markov model to estimate progression, regression and clearance rates that reproduced type-specific (HPV-16, 18, 6, 11) cumulative incidence of HPV persistent infection, CIN1, 2 and 3 at 12, 24 and 36 months available in Insinga et al. 2007[49]. The model includes 4 health states: HPV infection (without CIN), CIN1, CIN2 and CIN3 and women can clear the infection, progress or regress between the different grades of lesions. We simulated a cohort of women over time with a 1-month time step and we used the least square method to obtain the sets of parameters that minimized the difference between the observed and modeled cumulative incidence of CIN1, CIN2 and CIN3. To take into account the uncertainty surrounding the natural history parameters for each vaccine HPV-type (16, 18, 6, 11), we estimated parameter sets for 5 different scenarios. We estimated the parameter fit to the point estimates reported in Insinga et al. 2007[49] (scenario 1), and the upper and lower bounds

of the 95% confidence interval (scenario 2 and 3). We then varied the proportion of women censored after a CIN1+ diagnosis (scenario 4) and the proportion of lesions detected by screening (scenario 5). Our initial prior range for each natural history parameter was obtained by selecting the minimum and maximum values over the 5 different scenarios. These ranges were compared to those published by Jit et al. [50]. To be as inclusive as possible, we chose the Jit et al. parameter value as our minimum or maximum prior value if it was lower or higher than our estimated prior range. We assumed uninformative prior ranges for the natural history of cross-protective and not cross-protective types, given the scarcity of data to inform these parameters.

Data on the progression from CIN3 to SCC are scarce due to ethical reasons. Our prior range for the time interval between CIN3 and SCC (15 to 40 years) was based on data from Gustafsson 1997 et al.[51], which reported the age-specific incidence of cervical cancer prior to screening. In our model, each woman with CIN3 is given a time to SCC based on a normal distribution $N\left(\mu,\ \sigma = 0.3 \times \mu\right)$, where μ is the sampled average time interval between CIN3 and SCC.

Table A17 summarizes the prior ranges for the natural history parameters and Figures A20-28 represent the posterior parameter sets.

Table A17. Progression, regression and clearance rates for cervical intraepithelial lesions and squamous cervical cancer– Prior ranges

	HPV 16		HPV 18		HPV 6/11		HPV HR†		HPV Cross		HPV Not Cross	
	Rate (per w-y)		Relative rate (vs HPV 16)		Relative rate (vs HPV 16)		Relative rate (vs HPV 16)		Relative rate (vs HPV 16)		Relative rate (vs HPV 16)	
	MIN	MAX	MIN	MAX	MIN	MAX	MIN	MAX	MIN	MAX	MIN	MAX
Progressions												
Infected to CIN1	0.25	1.33	0.40	0.79	0.79	3.02			0.50	1.50	0.25	1.00
CIN1 to CIN2	0.07	3.84	0.81	1.61	0.00	0.00			0.50	1.50	0.25	1.00
CIN2 to CIN3	0.43	4.27	0.37	0.60	0.00	0.00			0.50	1.50	0.25	1.00
CIN3 to CC1	0.03	0.07										
Regressions												
Regression from CIN1	0.00	3.62	0.00	5.05	3.43	15.26	0.50	2.00				
% CIN1 regress to cleared	0.70	0.90										
CIN2 to CIN1	0.00	2.48	0.80	1.20	0.00	0.00	1.00	2.00				
CIN2 to cleared	0.00	1.89	0.79	1.19	0.00	0.00	1.00	2.00				
CIN3 to CIN2	0.00	0.00										

† HPV HR represents the cross-protective and not cross-protective types together. If there is a value in this category, it means that the cross-protective and non cross-protective types take exactly the same parameter for this health transition.

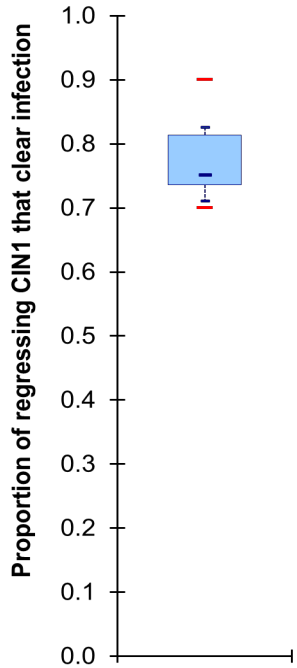


Figure A20. Proportion of regressing CIN1 that clear HPV infection – Posterior distribution. Box plots represent the medians, and 10, 25, 75, and 90th percentiles of the posterior parameter sets. Women regressing from CIN1 can either return to the infected or susceptible state. Red lines represent the minimum and maximum values of the prior range.

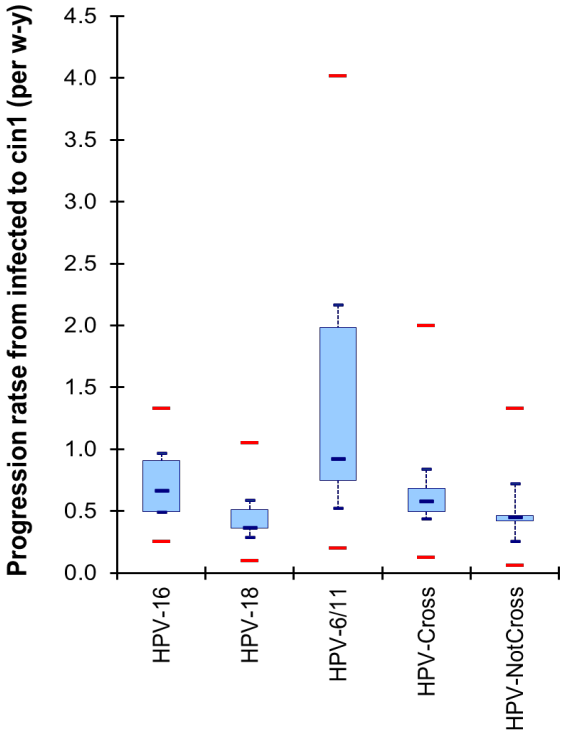


Figure A21. Progression rates from infected to CIN1 – Posterior distribution. Box plots represent the medians, and 10, 25, 75, and 90th percentiles of the posterior parameter sets. Red lines represent the minimum and maximum values of the prior ranges.

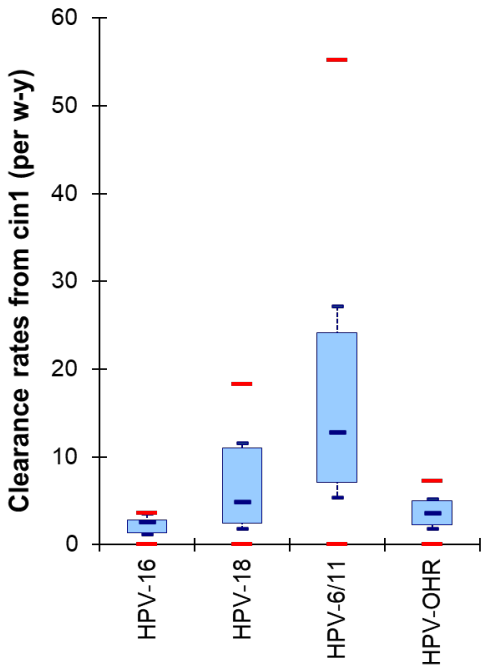


Figure A22. Clearance rates from CIN1 – Posterior distribution. Box plots represent the medians, and 10, 25, 75, and 90th percentiles of the posterior parameter sets. Red lines represent the minimum and maximum values of the prior ranges.

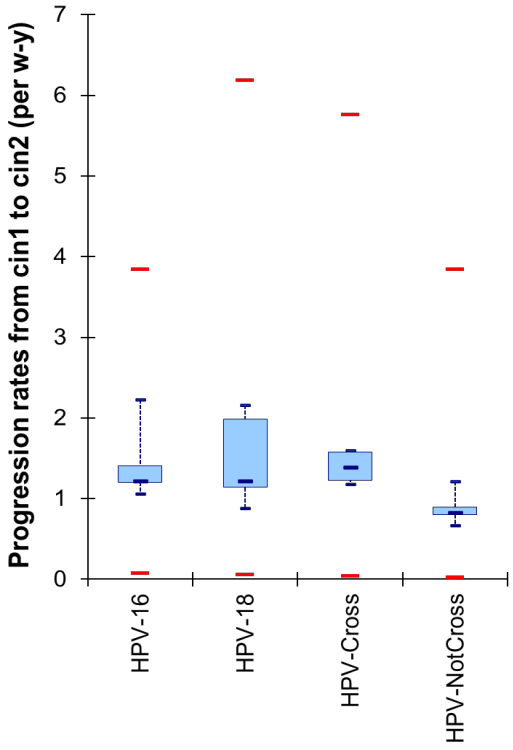


Figure A23. Progression rates from CIN1 to CIN2 – Posterior distribution. Box plots represent the medians, and 10, 25, 75, and 90th percentiles of the posterior parameter sets. Red lines represent the minimum and maximum values of the prior ranges.

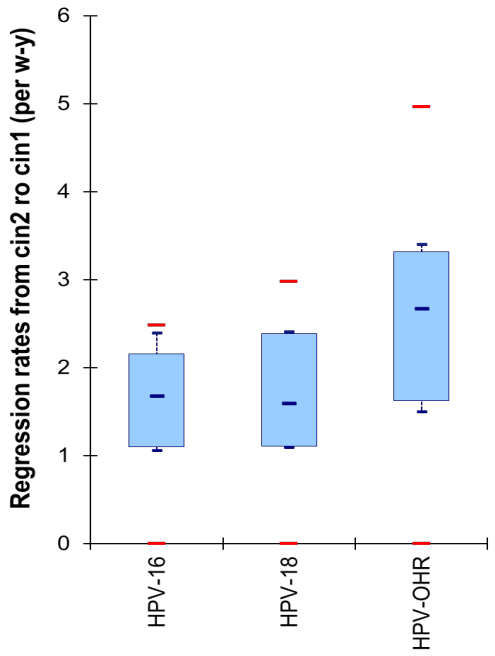


Figure A24. Regression rates from CIN2 to CIN1 – Posterior distribution. Box plots represent the medians, and 10, 25, 75, and 90th percentiles of the posterior parameter sets. Red lines represent the minimum and maximum values of the prior ranges.

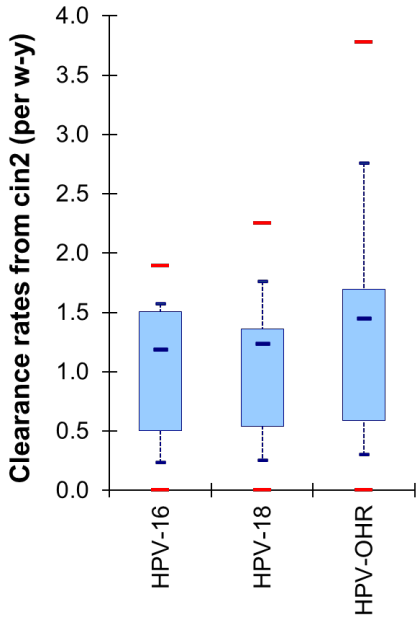


Figure A25. Clearance rates from CIN2 – Posterior distribution. Box plots represent the medians, and 10, 25, 75, and 90th percentiles of the posterior parameter sets. Red lines represent the minimum and maximum values of the prior ranges.

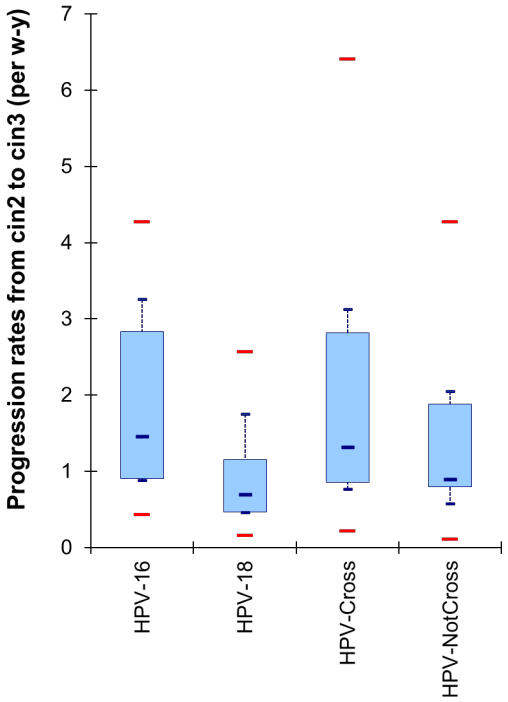


Figure A26. Progression rates from CIN2 to CIN3 – Posterior distribution. Box plots represent the medians, and 10, 25, 75, and 90th percentiles of the posterior parameter sets. Red lines represent the minimum and maximum values of the prior ranges.

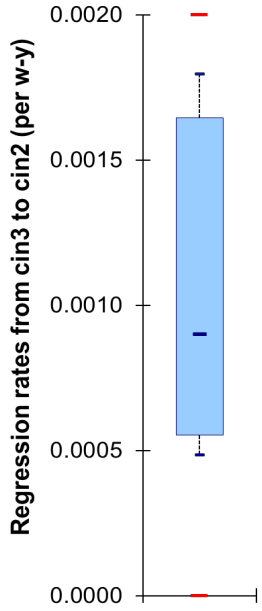


Figure A27. Regression rates from CIN3 to CIN2 – Posterior distribution. Box plots represent the medians, and 10, 25, 75, and 90th percentiles of the posterior parameter sets. Red lines represent the minimum and maximum values of the prior ranges.

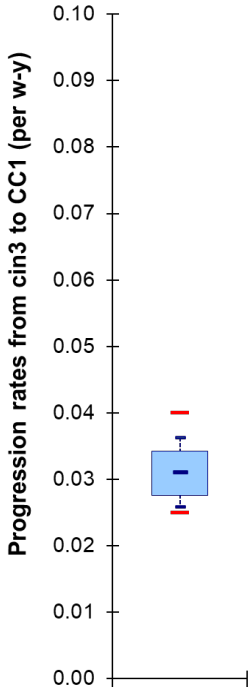


Figure A28. Progression rates from CIN3 to CC1 – Posterior distribution. Box plots represent the medians, and 10, 25, 75, and 90th percentiles of the posterior parameter sets. Red lines represent the minimum and maximum values of the prior ranges.

Progression, symptoms and mortality in cancer stages. Because virtually no data exist on the rate of progression from localized SCC through distant stage, we used the mean age at diagnosis of each cancer stage (available in the SEER database[52]) to approximate the delay between two consecutive cancer stages and then obtain the progression rates. We also used SEER data to obtain the stage-specific mortality rates. Finally, we used previously published estimates of the probability of developing symptoms from Myers et al.[53].

Table A18. Progression, symptoms and mortality in cancer stages - Parameters

	SCC I Local	SCC II Regional	SCC III Distant
Progression rates to next cancer stage (per women-year)	0.15	0.31	NA
Probability of developing symptoms	15.0%	40.0%	90.0%
Mortality rates (per women-year)	0.018	0.110	0.354

Anogenital warts (AGW) parameters. The proportion of HPV-6/11 leading to an AGW consultation was assumed to be dependent on age and gender. The median posterior parameter values of the proportion of HPV-6/11 infections leading to an AGW consultation for women (men) aged < 35 and 35+ years was 7% (6%) and 54% (56%), respectively.

Other HPV-related cancer parameters. In our model, each infected individual is given a probability of progressing towards cancer (type and gender-specific) and a time to cancer based on a normal distribution $N(\mu,\sigma)$, where μ is the sampled average time interval between persistent infection and cancer. A different probability distribution is estimated for adenocarcinomas, and cancers of the anus, oropharynx, vulva, vagina, and penis, and for each HPV-type. Table A19 summarizes the posterior parameter sets.

Table A19. Model parameters for other-HPV related cancers*

	Proportion of infections progressing toward cancer† (%)		Probability distribution of cancer‡ over time since infection $N(\mu,\sigma)$			
			Mean μ (years)		Standard deviation σ (years)	
	Med	80% Range	Med	80% Range	Med	80% Range
FEMALE						
Cervical Adenocarcinoma						
HPV-16	0.089	(0.075; 0.123)	40.9	(39.5; 41.7)	43.3	(41.4; 47.0)
HPV-18	0.167	(0.094; 0.260)	40.7	(39.3; 42.5)	45.2	(39.6; 49.7)
HPV-31	0.004	(0.003; 0.005)	40.2	(39.1; 41.6)	45.7	(41.0; 51.1)
HPV-33	0.004	(0.003; 0.005)	41.6	(40.2; 51.7)	45.7	(41.1; 50.5)
HPV-45	0.025	(0.018; 0.032)	40.3	(39.9; 41.7)	45.3	(41.3; 55.3)
HPV-52	0.004	(0.003; 0.005)	41.6	(40.0; 49.4)	45.6	(41.1; 50.3)
HPV-58	0.004	(0.000; 0.005)	41.6	(40.0; 49.3)	45.7	(41.2; 51.2)
Anal Cancer						
HPV-16	0.141	(0.120; 0.193)	106.9	(105.8; 109.7)	39.6	(39.1; 40.9)
HPV-18	0.027	(0.015; 0.042)	107.7	(104.5; 110.4)	40.0	(38.5; 41.1)
HPV-31	0.013	(0.009; 0.016)	105.8	(105.7; 110.8)	39.4	(39.0; 41.3)
HPV-33	0.017	(0.012; 0.021)	107.3	(105.4; 110.7)	39.9	(39.0; 41.3)
Oropharyngeal Cancer						
HPV-16	0.090	(0.074; 0.124)	48.5	(47.7; 49.0)	12.1	(12.1; 12.2)
HPV-18	0.001	(0.001; 0.002)	48.2	(48.1; 49.5)	12.2	(12.0; 12.3)
HPV-33	0.010	(0.007; 0.013)	48.2	(47.4; 49.0)	12.0	(11.9; 12.3)

MALE						
Anal Cancer						
HPV-16	0.059	(0.042; 0.075)	53.1	(50.4; 53.5)	16.1	(15.6; 16.4)
HPV-18	0.012	(0.005; 0.019)	53.7	(53.7; 53.7)	16.1	(16.1; 16.1)
HPV-31	0.007	(0.003; 0.009)	53.6	(53.6; 53.6)	16.1	(16.1; 16.1)
HPV-33	0.009	(0.004; 0.012)	53.4	(53.4; 53.4)	15.9	(15.9; 15.9)
Oropharyngeal Cancer						
HPV-16	0.244	(0.170; 0.308)	46.6	(44.4; 47.2)	10.0	(9.6; 10.2)
HPV-18	0.004	(0.002; 0.006)	46.3	(46.3; 46.3)	10.0	(10.0; 10.0)
HPV-33	0.033	(0.016; 0.045)	47.4	(44.9; 47.4)	10.1	(10.1; 10.6)

*. The values shown in this table should not directly be interpreted as biological processes. In the absence of epidemiological data on natural history, these parameters were estimated in order for the model to reproduce the observed incidence of HPV-related cancers given age-specific type specific HPV incidence of infection.
†. In our model, not all infections "progressing toward cancer" will result in cancer due to competing risks of natural mortality.
‡. Without competing risks such as natural mortality or mortality related to other HPV cancers
Med: Median value of simulations; 80% Range: 10th and 90th percentiles of simulations

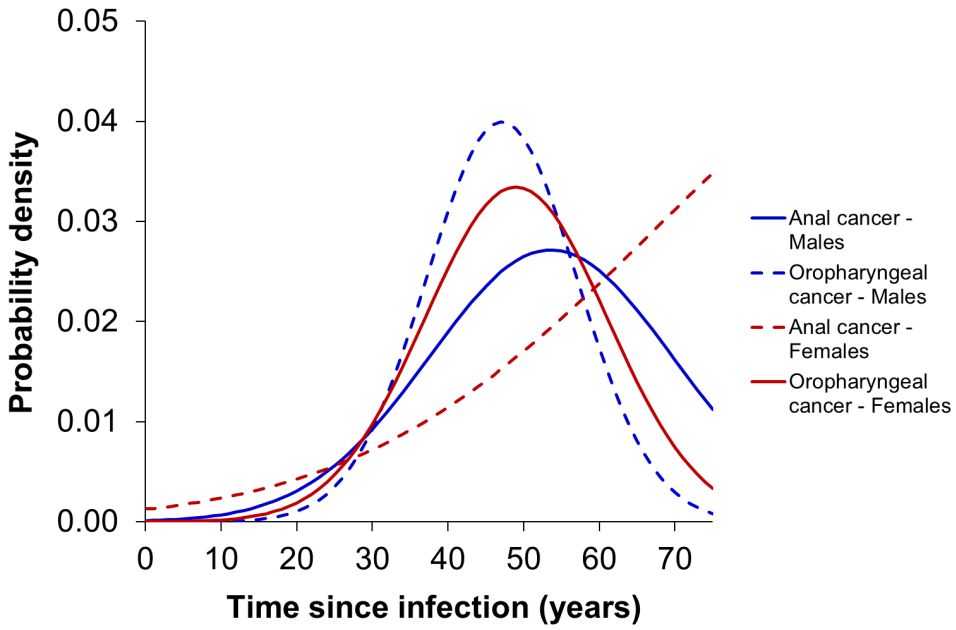


Figure A29. Examples of probability functions of HPV-16 related anal and oropharyngeal cancer over time since infection. Of note: In the model, these distributions are truncated due to natural mortality.

2.2.4 Screening Parameters

Screening parameters are based on data from the Manitoba cervical cancer screening program registry (MCCSP)[7] and on self-reported data collected with the Canadian Community Health Survey, Cycle 3.1, 2006[38]. The MCCSP collects information on all

cervical cytology performed in Manitoba since 1984. The registry holds information on demographic, cervical cytology result, histological result, diagnosis and recommended treatment. We worked in close collaboration with epidemiologists from the MCCSP to obtain detailed data on the frequency of routine cervical cancer screening. The CCHS is a national, cross-sectional, population-based survey conducted by Statistics Canada that provides information about the health status, health care utilization and health determinants of Canadians. More specifically, the CCHS collects information about the participation in cervical cancer screening (having ever had a Pap smear, delay since the last smear).

Proportion of women in screening behavior levels. The parameters for the proportion of women in the different screening behavior levels in Table A20 were calculated from the MCCSP and the CCHS. We assumed that women in screening behavior levels 0, 1, 2, and 3 have time intervals between two routine screening tests (i.e., the time between a normal cytology result and the previous one) of <2 years, 2-4.9 years, 5-9.9 years, and ≥ 10 years. Level 4 represents women who will never be screened in their lifetime. The proportion of women in each level of screening behavior was calculated using data from the MCCSP. However, since data from the screening registry only contains information about women who are registered in the MCCSP (i.e. women who have had a cervical screening test), we then complemented these data with information from the CCHS to have an estimate of the proportion of women who have never been screened (level 4).

Table A20. Proportion of women in the screening behavior levels - Parameters

	S = 0	*S* = 1	*S* = 2	*S* = 3	*S* = 4
Interval	Short (< 2 yrs)	Medium (2–4.9 yrs)	Long (5-9.9 yrs)	Very long (≥ 10 yrs)	Never
	0.36	0.33	0.15	0.10	0.07

Onset of cervical cancer screening. The parameters for the onset of cervical screening were obtained from the MCCSP. Using the cohort of women who had a screening test in 2004, we identified those who had no previous screening test recorded in the registry for the previous 20 years. We used the distribution of the total population of women in Manitoba, in each age group, as the denominator to estimate the proportion of women who had a first screening at each age. Based on this distribution, each woman in the model

is attributed a first screening appointment. We assume that the age at start of cervical screening was independent of the screening behavior.

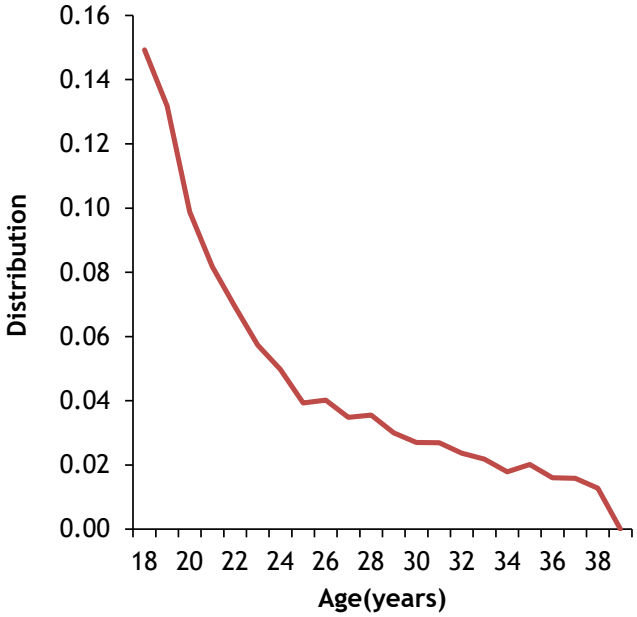


Figure A29. Age distribution at onset of cervical screening - Parameters.

Screening rate. The screening rate represents the rate of routine screening tests (i.e. excludes screening tests performed for the follow-up of abnormal results). The parameters for the screening rate were calculated from the MCCSP data. They are dependent on the level of screening behavior of women but are independent of age. Screening rates are obtained by the reciprocal of the mean delay between two consecutive routine screening tests.

Table A21. Screening rates (per person-year) – Parameters

	S = 0 Short (< 2 yrs)	*S* = 1 Medium (2–4.9 yrs)	*S* = 2 Long (5-9.9 yrs)	*S* = 3 Very long (≥ 10 yrs)	*S* = 4 Never
Mean delay between 2 routine screening	1.25 yrs	3.11 yrs	6.94 yrs	12.00 yrs	NA
Screening rate	0.80	0.32	0.14	0.08	0.00

Screening performance for the detection of cervical lesions. Parameters for the probabilities of detecting women in each neoplastic state by cervical cytology were estimated using the data of two systematic reviews on psychometric performance of cervical cancer screening with cytology [54,55]. More specifically, in Nanda et al. [54], we used

data collected in low HPV prevalence settings and corrected for verification bias whereas in Arbyn et al. [55] we used data presented for conventional cytology. We complemented these data with information from two studies presenting the specific cytological result obtained by women diagnosed with an invasive cancer [56,57]. Given uncertainty around the estimates of sensitivity and specificity, we used the 95% confidence intervals provided in the papers to obtain a range of probabilities. When confidence intervals were unavailable, we varied the point estimate by ±10%. We conducted extensive preliminary sensitivity analyses within the estimated range of probabilities. The higher sensitivity and specificity estimates (underlined parameter values in Table A22) were required in order for the model to come close to fitting the age-specific incidence of LSIL/HSIL in Canada [5,7].

Table A22. Probabilities of detecting a neoplastic state by cytology – Parameters

	Cytological results					
Health States	**Normal %**	**ASCUS %**	**LSIL %**	**HSIL/ASC-H+ %**	**Cancer %**	**Total %**
Normal	97.0 (95.0-99.0)	1.5 (0.5-2.0)	1.0 (0.5-1.5)	0.45 (0.0-1.0)	0.05 (0.0-0.5)	100.0
CIN1	41.0 (37.0-45.0)	12.0 (10.5-14.5)	29.0 (26.5-32.5)	18.0 (16.0-18.0)	0.0 (0.0-0.0)	100.0
CIN2/3	20.0 (18.0-22.0)	5.0 (3.0-7.0)	20.0 (18.0-22.0)	54.0 (48.0-58.0)	2.0 (1.0-3.0)	100.0
Cancer	0.0 (0.0-2.0)	6.0 (2.0-9.0)	9.0 (3.0-12.0)	54.0 (50.0-60.0)	31.0 (27.0-35.0)	100.0

Parameters for the probabilities of confirming the neoplastic state by colposcopy / biopsy were estimated using the data from several articles assessing the success of colposcopy at diagnosing CIN or the inter- intra-observer agreement in CIN diagnosis [58-62]. Given that sensitivity estimates of colposcopy / biopsy to diagnose CIN highly depends on the number and location of biopsies taken [58], we considered a wide range of probabilities to account for different biopsy practices. Similarly to cytological screening, we conducted preliminary analysis within the estimated range of probabilities and concluded that scenarios using the highest sensitivity and specificity of colposcopy were those who reproduced the best the observed incidence of CIN and cervical cancer in Canada[5,7].

Table A23. Probabilities of diagnosing a neoplastic state by colposcopy/biopsy – Parameters

	Colposcopy/biopsy results					
Health States	**Normal**	**CIN1**	**CIN2**	**CIN3**	**Cancer**	**Total**
Normal	88.0% (65-100)	7.0% (0-28)	3.0% (0-5)	2.0% (0-2)	0.0% (0-0)	100.0%
CIN1	22.0% (10-38)	62.0% (57-90)	15.0% (0-3)	1.0% (0-2)	0.0% (0-0)	100.0%
CIN2	8.0% (5-19)	10.0% (5-13)	47.0% (52-90)	35.0% (0-16)	0.0% (0-0)	100.0%
CIN3	8.0% (1-19)	10.0% (3-13)	16.0% (6-16)	56.0% (42-90)	10.0% (0-10)	100.0%
Cancer	0% (0-0.5)	0.0% (0-2)	0.0% (0-2.5)	5.0% (0-5)	95.0% (90-100)	100.0%

Management of women with abnormal results. The parameters for the follow-up of abnormal cytology results are based on current guidelines for the follow-up of abnormal cytology results in Canada[16-18] and on empirical data on the follow-up of abnormal cytology results collected in Manitoba (CancerCare Manitoba registry) [7] and in the province of Quebec [63]. More specifically, based on data collected in Quebec, we assumed that a small proportion of women would be lost to follow-up and would return to routine screening without changing the natural history of their disease. Although the recommended follow-up for a first ASC-US or LSIL is a repeat cytology in Canada, we observed that in Québec and Manitoba a small proportion of women are referred directly to colposcopy [7,63]. Following a repeat abnormal result, we assumed that 100% of women are referred to colposcopy.

Finally, based on a Cochrane systematic review on the efficacy of seven alternative surgical treatments for CIN[64], we assumed that treatment fails for 5% of women (the health state of these women remains unchanged after treatment). Using data from Kreimer et al [65], we assumed that 80% of women clear both the lesion and the infection after treatment and 15% clear the lesion but remain HPV infected.

Table A24. Parameters for the management of women with a first or repeated abnormal cytology result, according to the severity of the result - Parameters.

	First abnormal result				Repeat abnormal result			
Follow-up	ASCUS	LSIL	HSIL/ ASC-H	SCC	ASCUS	LSIL	HSIL/ ASC-H	SCC
Lost to follow-up	12.7%	8.9%	4.5%	0.0%	0.0%	0.0%	0.0%	0.0%
Repeat cytology	84.3%	85.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Colposcopy/biopsy	3.0%	6.1%	95.5%	100.0%	100.0%	100.0%	100.0%	100.0%

2.2.5 HPV type-specific positivity in cervical and non-cervical cancers

We performed a review of the literature to obtain the HPV type distributions in cervical and non-cervical cancers for North America. We identified 3 meta-analysis containing worldwide data on HPV prevalence in non-cervical cancers (Backes et al.[25], De Vuyst et al.[24] and Kreimer et al.[26]) and we calculated North-American HPV prevalences using country-specific data available in the Appendix of these articles. We also obtained North-American estimates of HPV prevalence in cervical cancer stratified by histological type from Dr Gary Clifford (International Agency for Research in Cancer). Table A25 presents the North-American HPV type distributions in HPV-related cancers used to estimate the long-term impact of HPV vaccination on other HPV-related cancers (see Section 2.2.5).

Table A25. HPV type-specific positivity in cervical and non-cervical cancers - Parameters.

Cancers	**Cervical (ALL)**	**SCC**	**Adeno**	**Vulvar**	**Vagina**	**Anal**	**Penile**	**Oral cavity**	**Oropharynx**	**Larynx**
References	Clifford[a]	Clifford[a]	Clifford[a]	De Vuyst[24]	De Vuyst[24]	De Vuyst[24]	Backes [25]	Kreimer[26]	Kreimer[26]	Kreimer[26]
	%	%	%	%	%	%	%	%	%	%
Any HPV	100	100	100	66	70	83	49	16	47	14
HPV16	61	66	47	78	84	85	92	62	90	73
HPV 18	21	13	47	7	15	9	5	17	1	24
HPV 31	4	5	1	1	0	3	5	0	0	9
HPV 33	4	5	1	12	0	5	2	7	5	0
HPV 45	5	5	6	3	0	0	3	0	0	0
HPV 52	2	2	1	0	0	0	0	0	0	0
HPV 58	1	1	1	0	0	0	0	0	0	0
HR not cross	7	7	2	0	0	0	0	0	0	0
HPV 6	0	1	0	0	0	0	0	0	0	0
HPV 11	0	0	0	0	0	0	0	0	0	0

a. Personal communication Dr. Gary Clifford (IARC, CliffordG@iarc.fr)

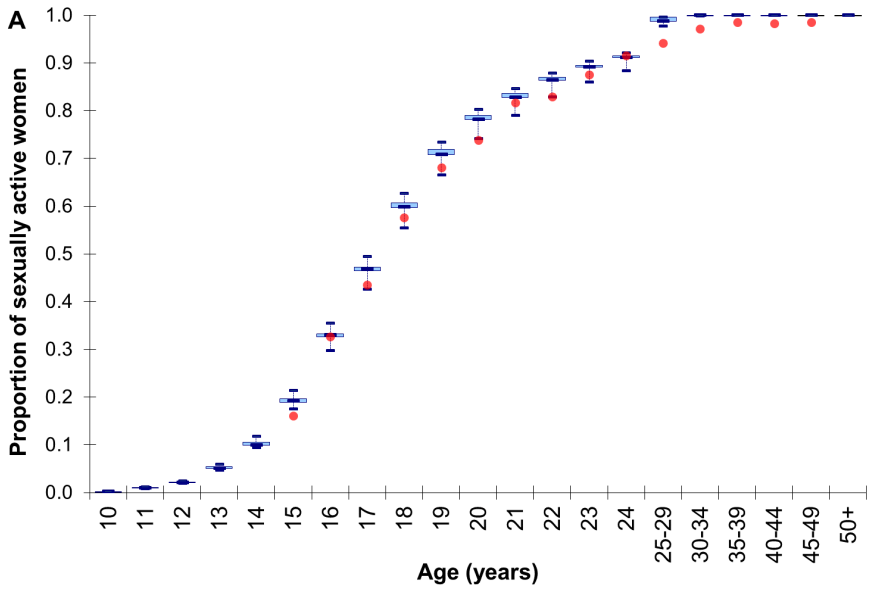
2.2.6 MSM model parameters

We estimated the age-specific fractions of disease incidence attributable to MSM using the proportion of men that are MSM and the relative risk of HPV related diseases among MSM compared to heterosexual men. Based on data from the literature, we assumed MSM represent 3% of the male population[37], that MSM are 17 times more at risk for anal cancer than heterosexual men[31] and three times more at risk for AGW or penile and oropharyngeal cancers[32].

2.3 Model fit

Please see Table A1 for details on the data used to fit the model (stratifications, references and number of data points), and Section 2.6 for target definitions. Figures A30-A32, A33-A37, A38-A40, A41-43, and A44 illustrate the model fit to sexual behavior, HPV prevalence, screening and cervical cancer, HPV type-specific positivity in CIN and SCC samples, and anogenital warts data, respectively.

2.3.1 Examples of fit to sexual behavior data



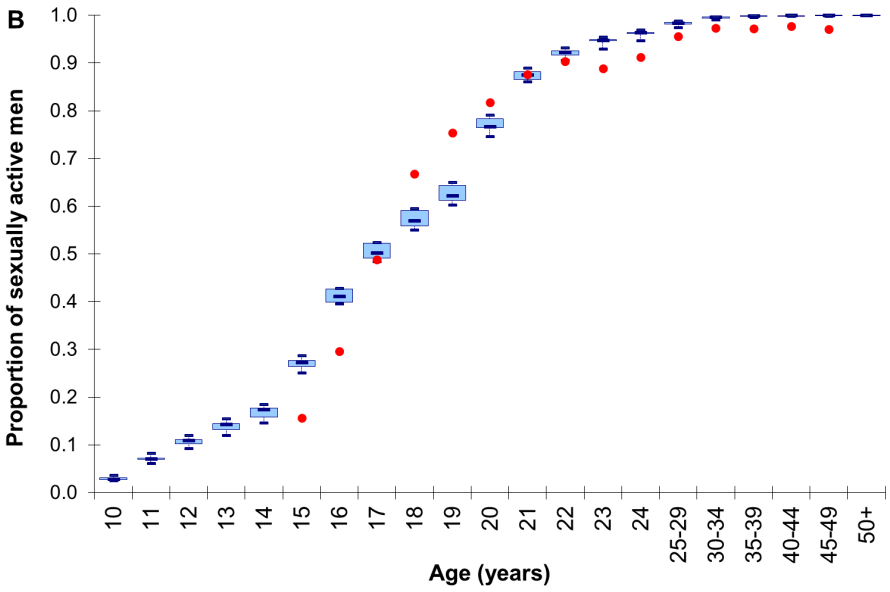


Figure A31. Proportion of sexually active A) women and B) men. Box plots represent the minimum, maximum and the 25, 50 and 75th percentiles of the model predictions generated by the posterior parameter sets. Dots represent observed data[27].

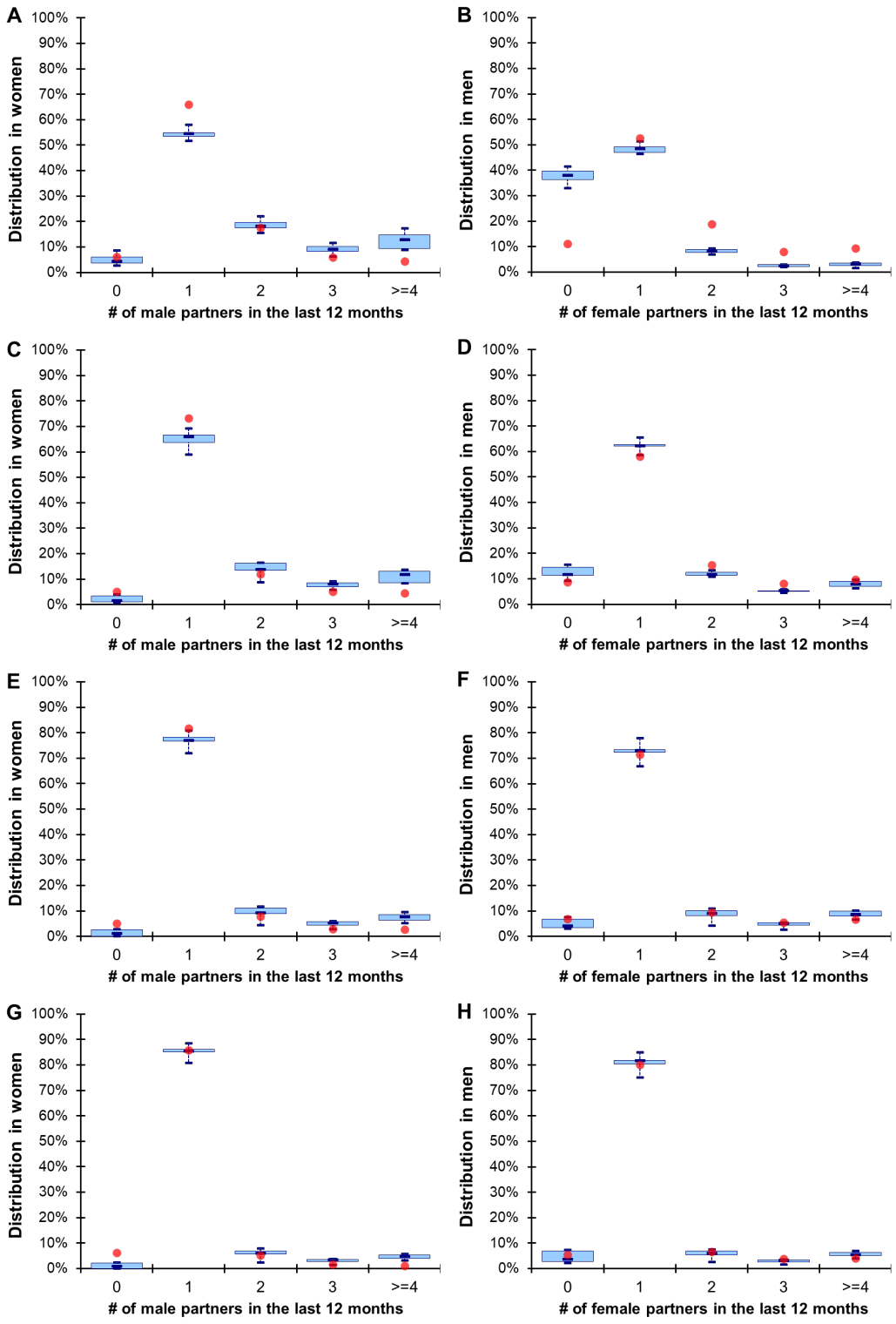


Figure A32. Number of partners in the last 12 months in sexually active women and men aged A-B) 15-19 yrs, C-D) 20-24 yrs, E-F) 25-29 yrs, and G-H) 30-34 yrs. Box plots represent the minimum, maximum and the 25, 50 and 75th percentiles of the model predictions generated by the posterior parameter sets. Dots represent observed data[27].

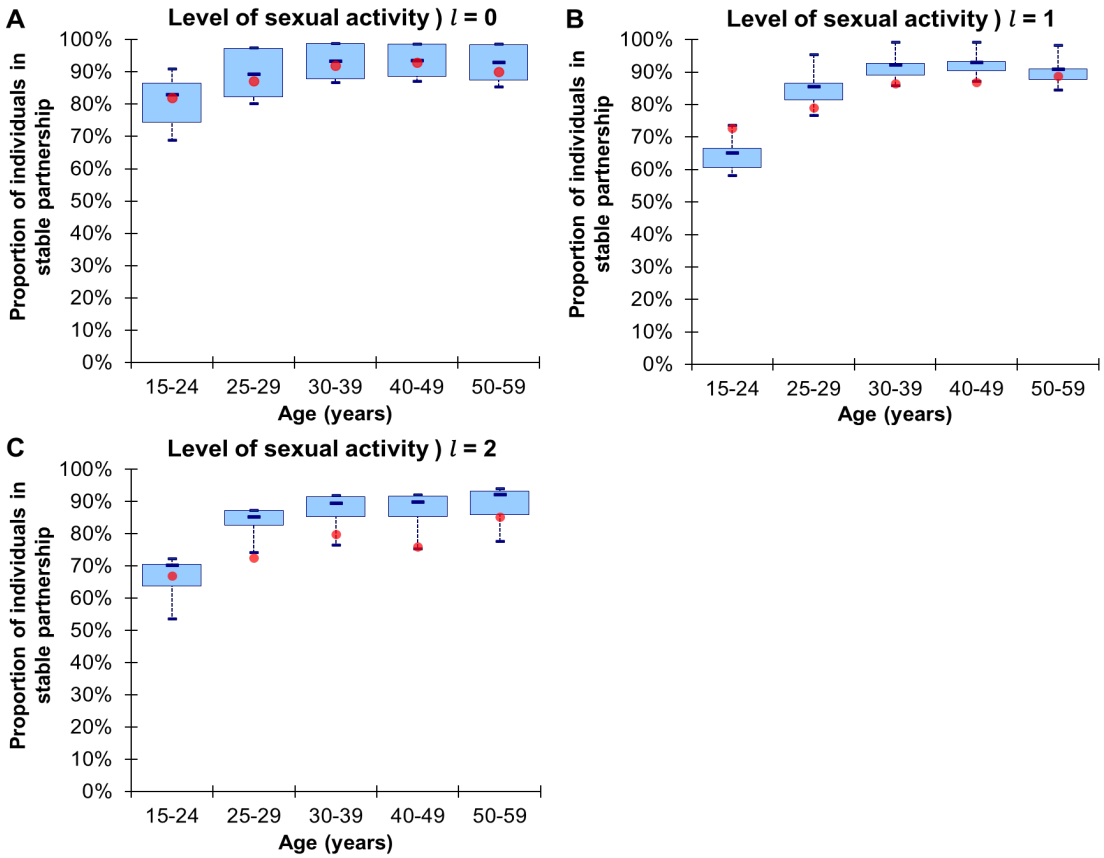


Figure A33. Percentage of women in a stable partnership in levels of sexual activity A) $l = 0$, B) $l = 1$ and C) $l = 2$. Box plots represent the minimum, maximum and the 25, 50 and 75th percentiles of the model predictions generated by the posterior parameter sets. Dots represent observed data[28,29].

2.3.2 Examples of fit to HPV prevalence data

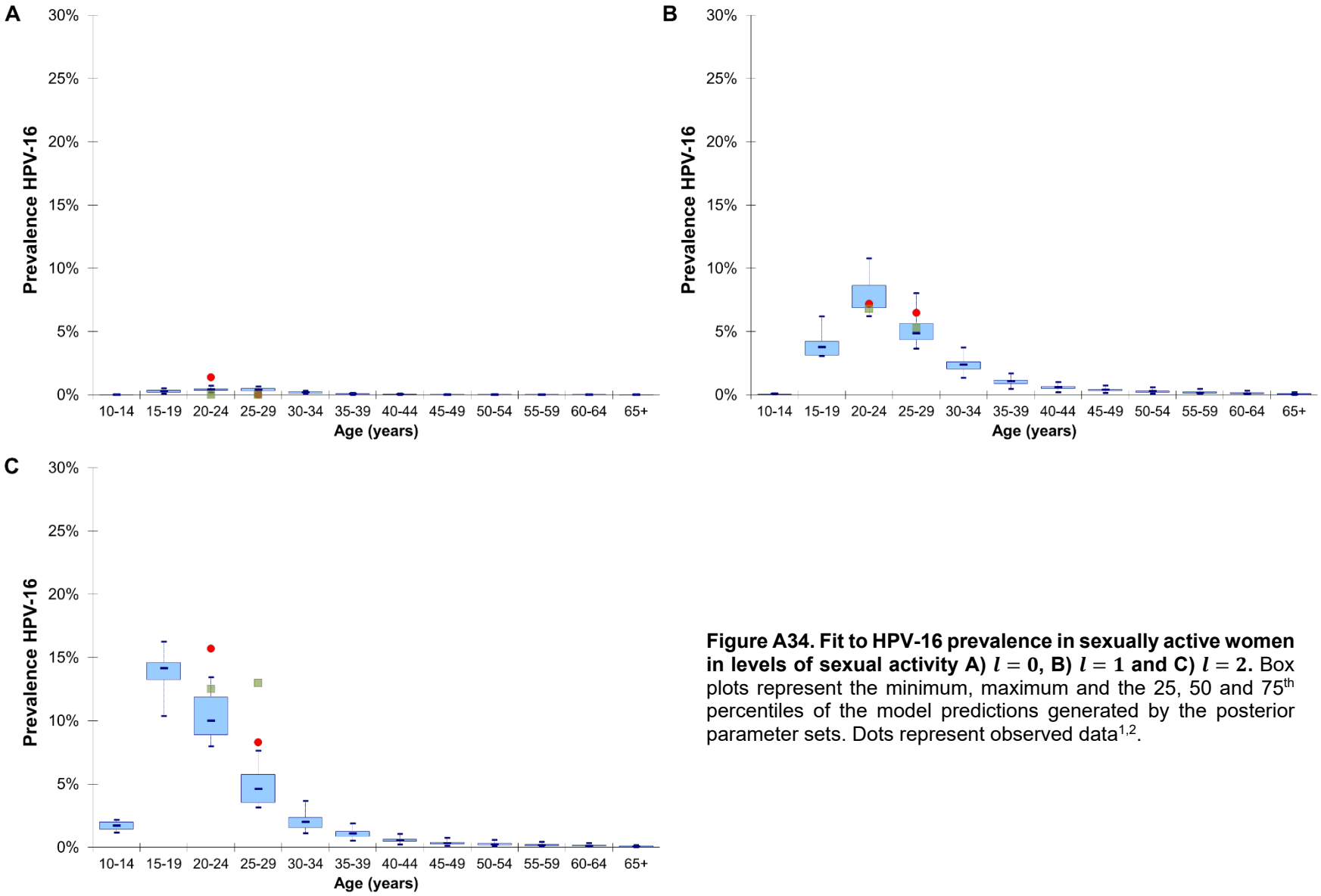


Figure A34. Fit to HPV-16 prevalence in sexually active women in levels of sexual activity A) $l = 0$, B) $l = 1$ and C) $l = 2$. Box plots represent the minimum, maximum and the 25, 50 and 75th percentiles of the model predictions generated by the posterior parameter sets. Dots represent observed data[1,2].

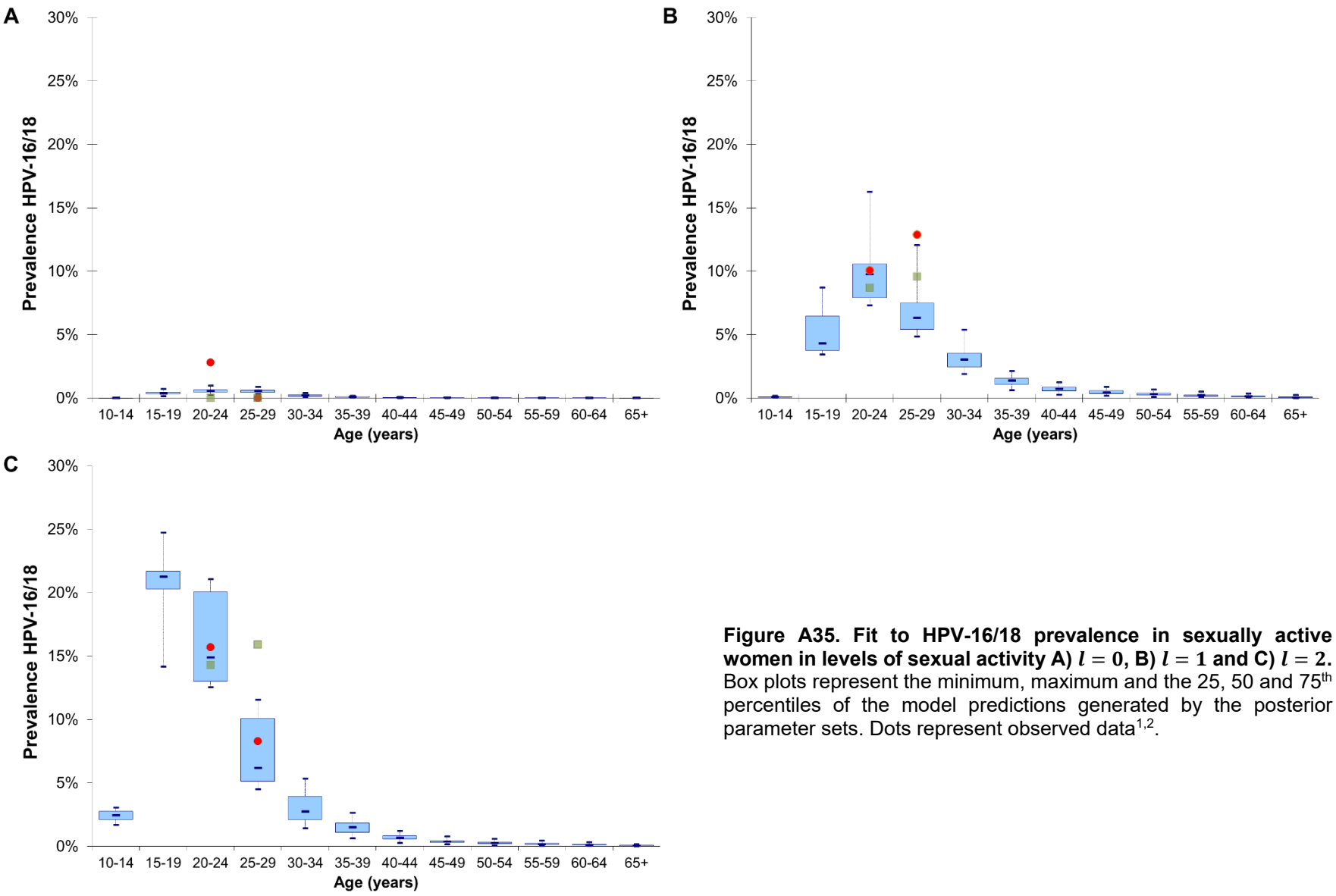


Figure A35. Fit to HPV-16/18 prevalence in sexually active women in levels of sexual activity A) $l = 0$, B) $l = 1$ and C) $l = 2$. Box plots represent the minimum, maximum and the 25, 50 and 75th percentiles of the model predictions generated by the posterior parameter sets. Dots represent observed data[1,2].

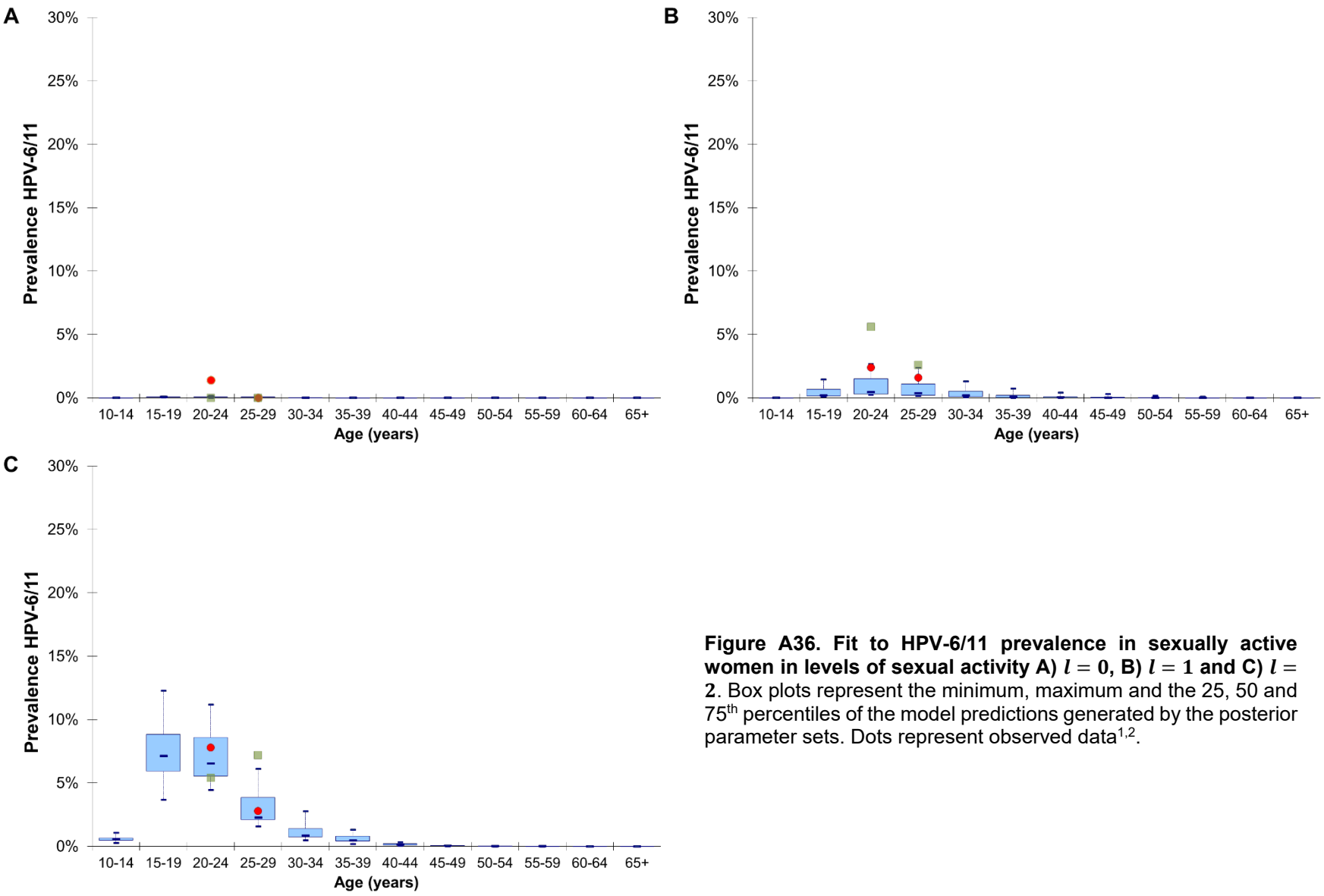


Figure A36. Fit to HPV-6/11 prevalence in sexually active women in levels of sexual activity A) $l = 0$, B) $l = 1$ and C) $l = 2$. Box plots represent the minimum, maximum and the 25, 50 and 75th percentiles of the model predictions generated by the posterior parameter sets. Dots represent observed data[1,2].

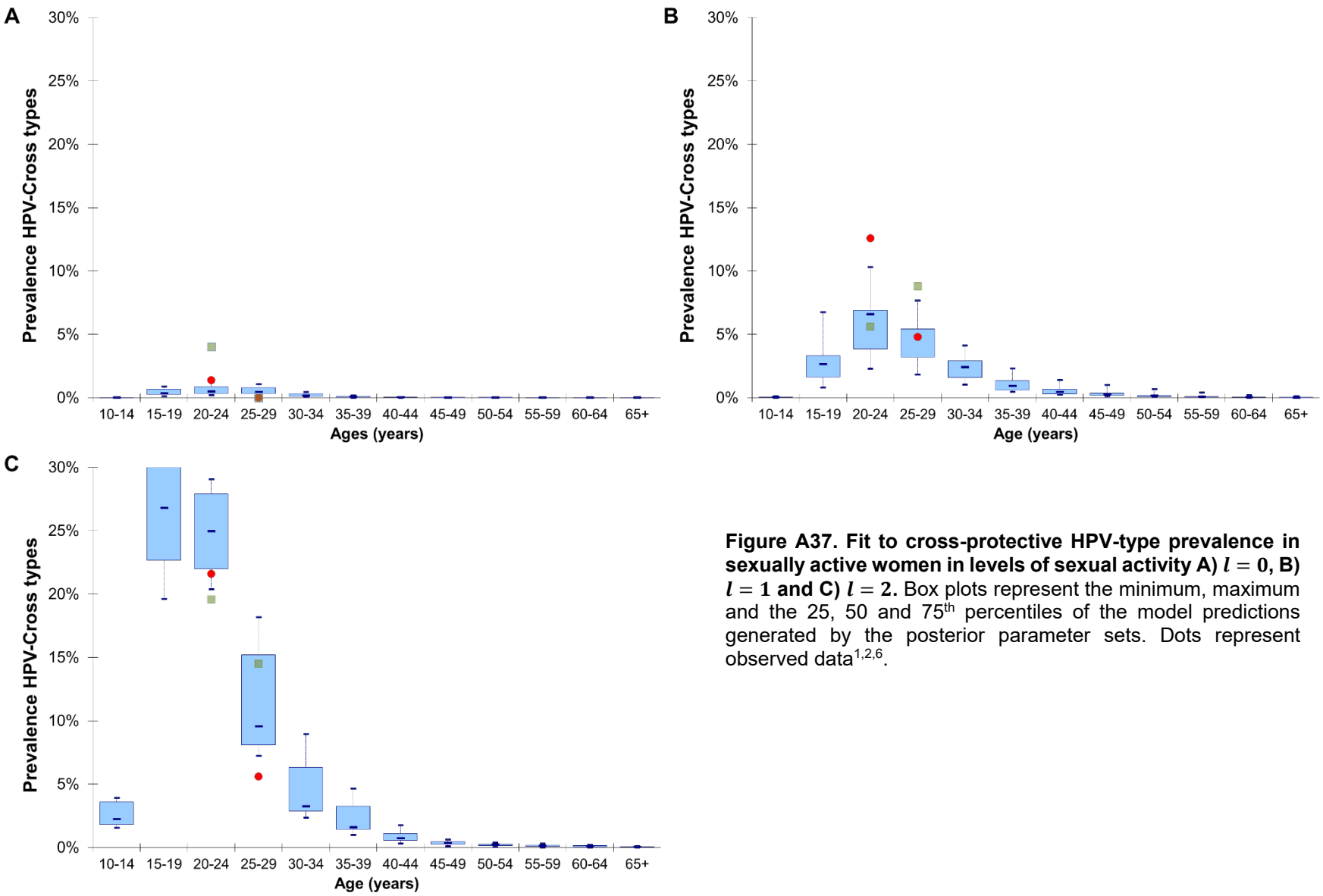


Figure A37. Fit to cross-protective HPV-type prevalence in sexually active women in levels of sexual activity A) $l = 0$, B) $l = 1$ and C) $l = 2$. Box plots represent the minimum, maximum and the 25, 50 and 75th percentiles of the model predictions generated by the posterior parameter sets. Dots represent observed data[1,2,6].

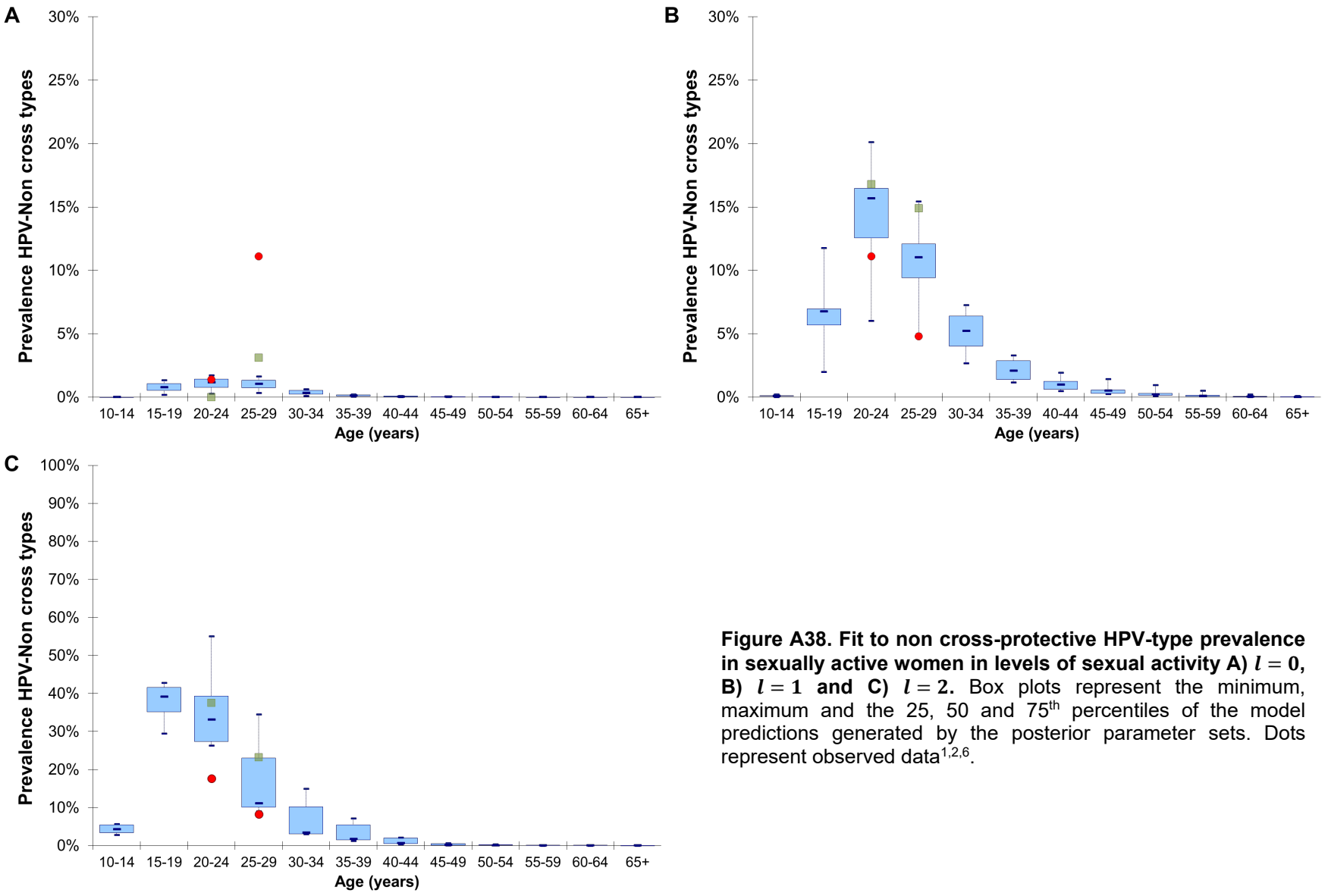


Figure A38. Fit to non cross-protective HPV-type prevalence in sexually active women in levels of sexual activity A) $l = 0$, B) $l = 1$ and C) $l = 2$. Box plots represent the minimum, maximum and the 25, 50 and 75th percentiles of the model predictions generated by the posterior parameter sets. Dots represent observed data[1,2,6].

The model also fits the prevalence of HPV-6 and overall HR HPV by age and level of sexual activity[1,2,6] (data not shown).

2.3.3 Examples of fit to screening data

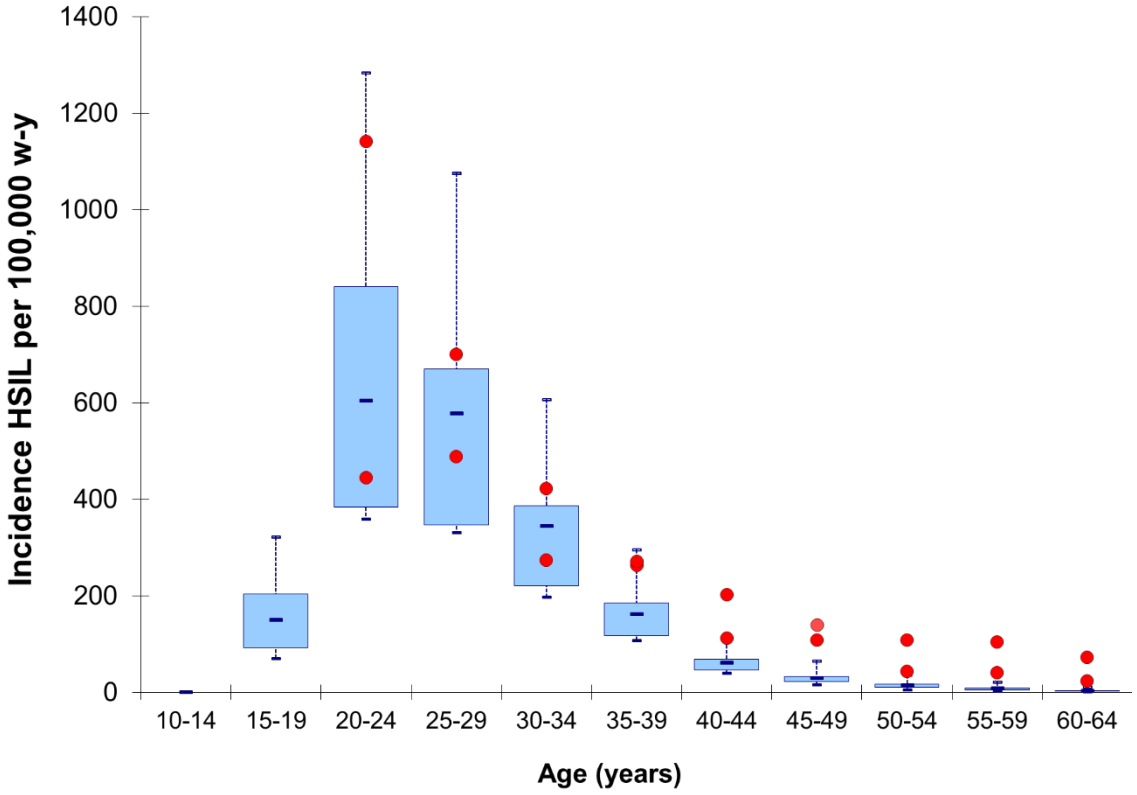


Figure A39. Incidence of HSIL over age. Box plots represent the minimum, maximum and the 25, 50 and 75th percentiles of the model predictions generated by the posterior parameter sets. Dots represent the minimum and maximum value of the observed data [5,7].

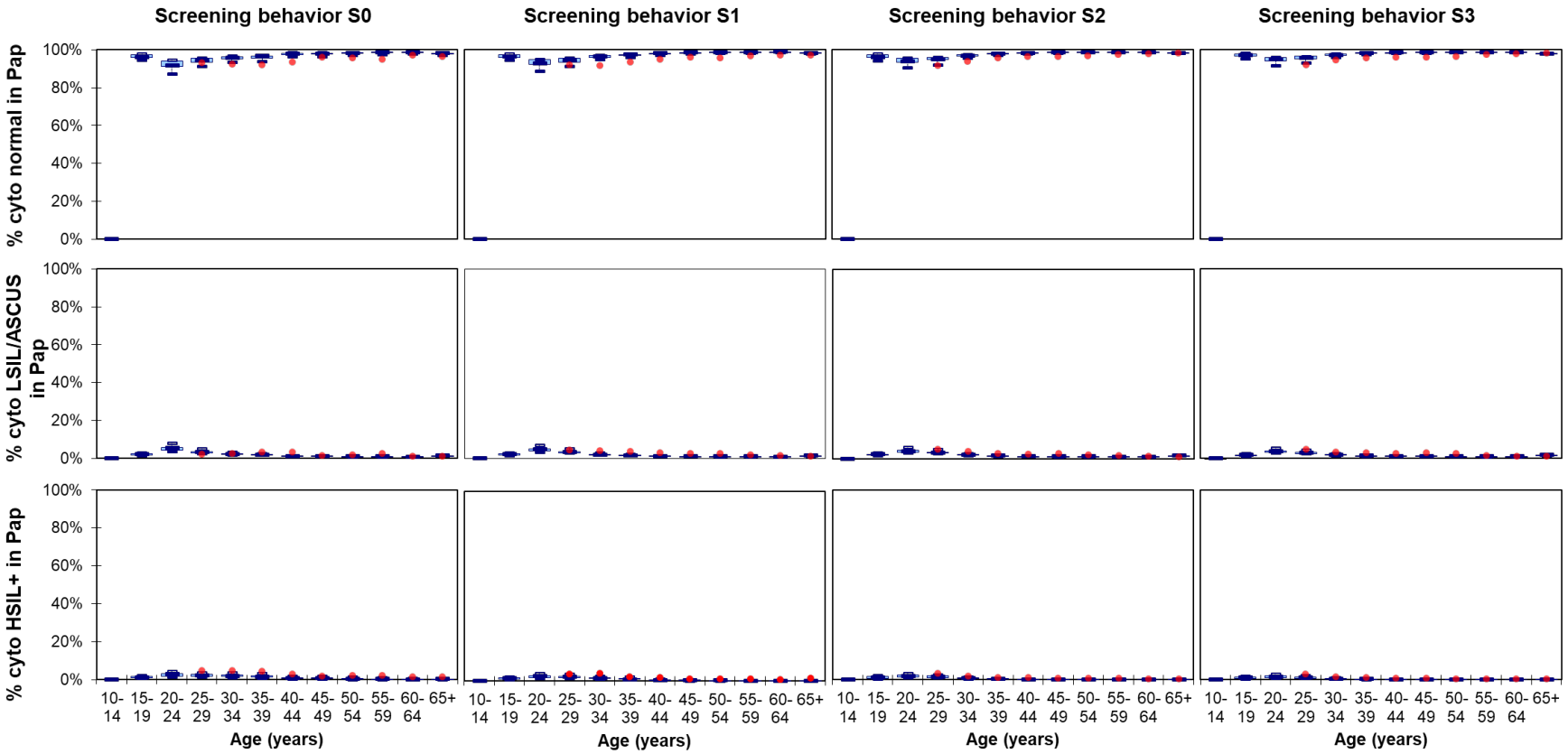


Figure A40. Percent of Pap results that are normal, LSIL/ASCUS and HSIL+ by level of screening behavior. Box plots represent the minimum, maximum and the 25, 50 and 75th percentiles of the model predictions generated by the posterior parameter sets. Dots represent observed data[5,7].

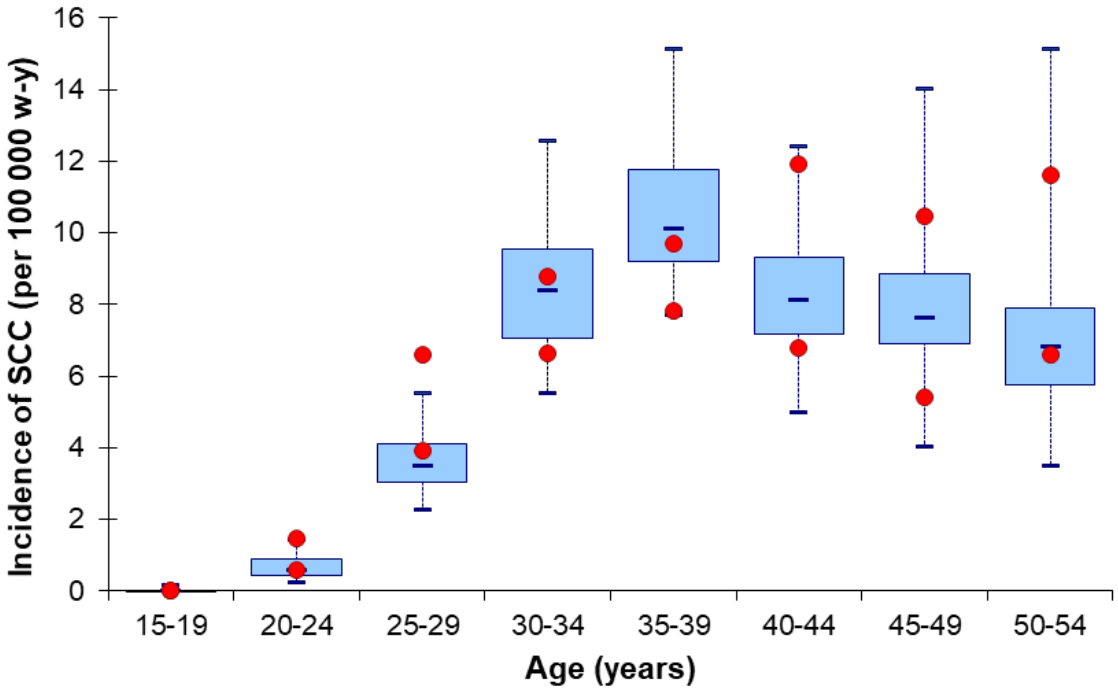


Figure A41. Cervical cancer incidence (squamous cell carcinoma - SCC). Box plots represent the minimum, maximum and the 25, 50 and 75th percentiles of the model predictions generated by the posterior parameter sets. Dots represent the minimum and maximum value of the observed data [3-5].

The model also fits the data on the incidence of ASCUS/LSIL by age[5,7] and the proportion of women ever screened by age[27] (data not shown).

2.3.4 Examples of fit to HPV type-specific positivity in CIN and SCC samples

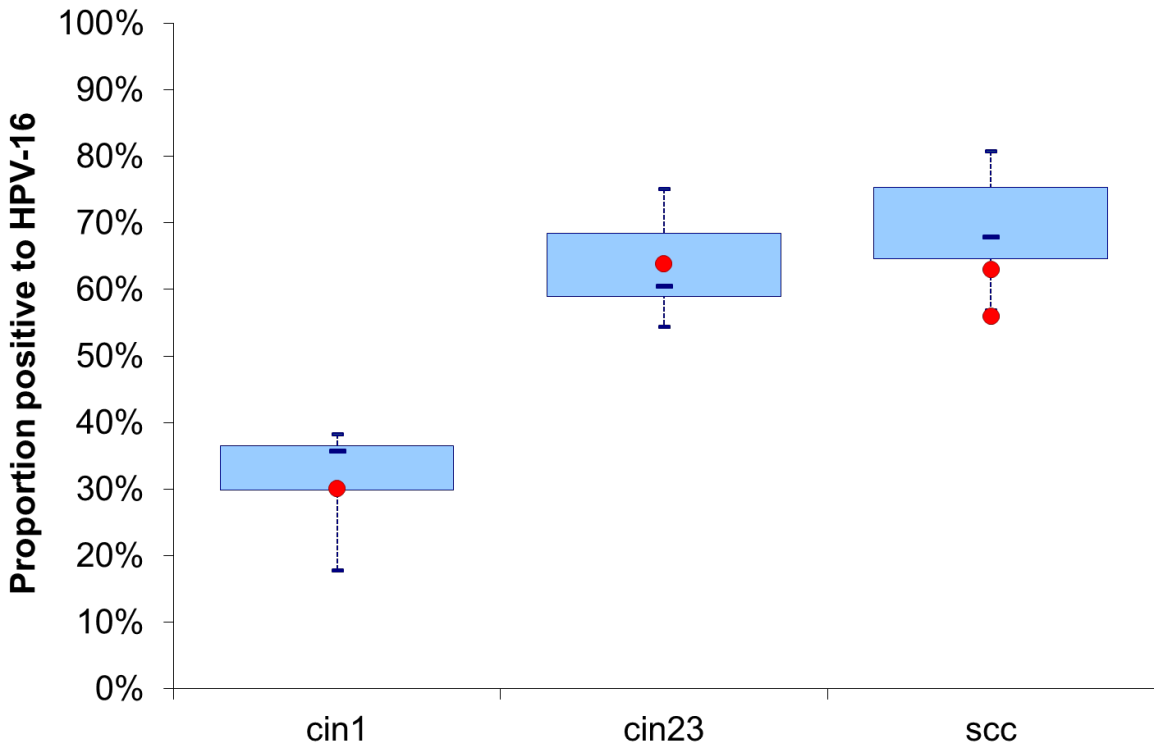


Figure A42. Proportion of diagnosed CIN and SCC with detected HPV-16. Box plots represent the minimum, maximum and the 25, 50 and 75th percentiles of the model predictions generated by the posterior parameter sets. Dots represent observed data for CIN1 and CIN2/3[30], and the minimum and maximum values of the observed data for SCC [31,64-66].

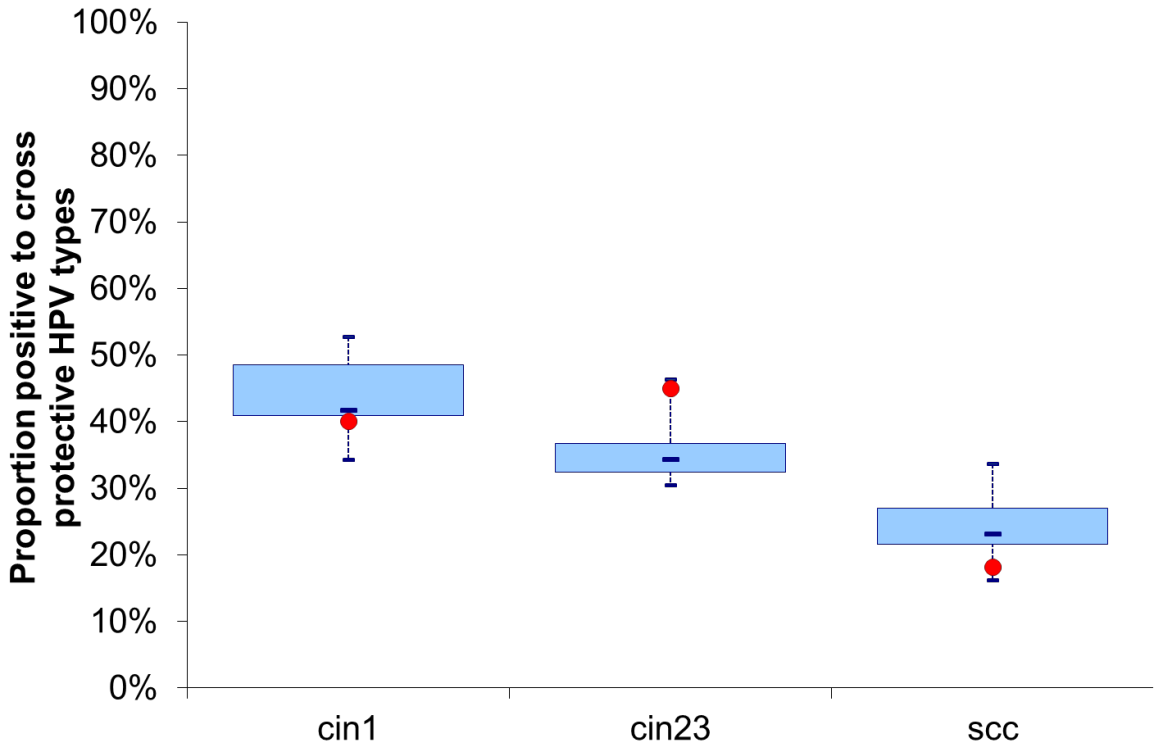


Figure A43. Proportion of diagnosed CIN and SCC with detected cross-protective HPV types. Box plots represent the minimum, maximum and the 25, 50 and 75th percentiles of the model predictions generated by the posterior parameter sets. Dots represent the observed data [30,31].

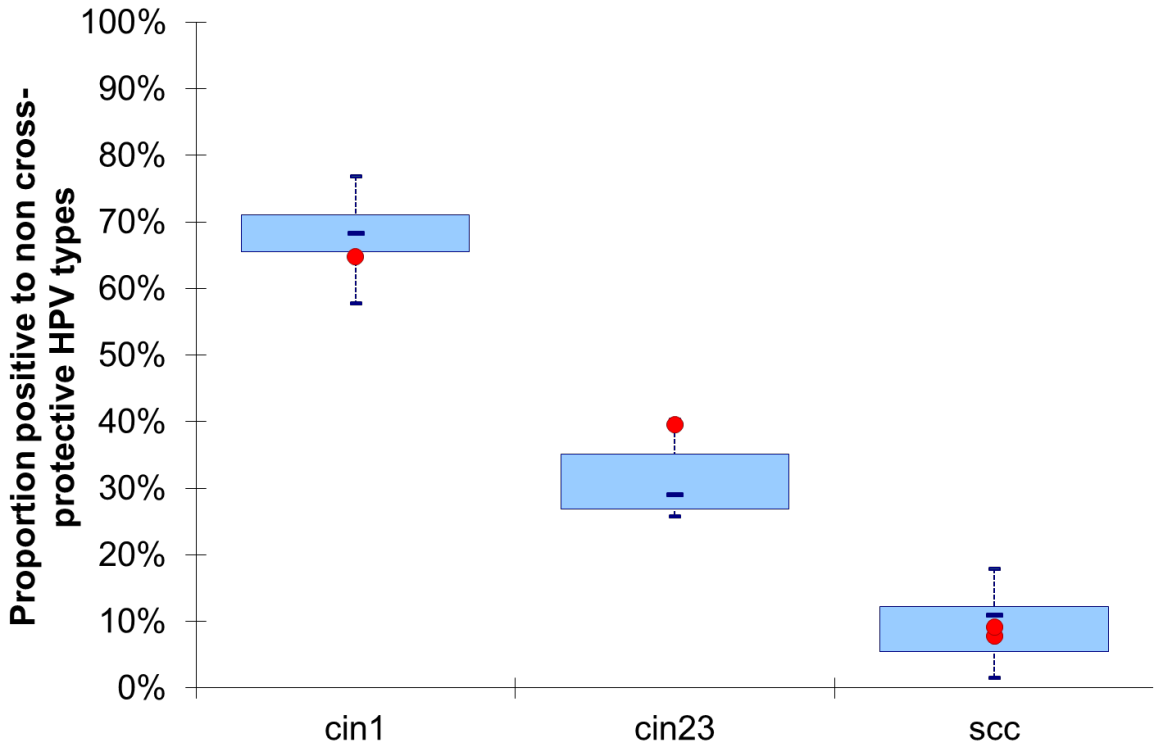


Figure A44. Proportion of diagnosed CIN and SCC with detected non cross-protective HPV types. Box plots represent the minimum, maximum and the 25, 50 and 75th percentiles of the model predictions generated by the posterior parameter sets. Dots represent the observed data[30,31].

The model also fits the proportion of diagnosed CIN with detected HPV-18, HPV-6 and HPV-11[30] and the proportion of diagnosed SCC with detected HPV-18[31] (data not shown).

2.3.5 Examples of fit to anogenital warts data

The model fits the incidence of anogenital warts (AGW) consultations in Manitoba[22]. For these fits, we assume that 85% of AGW consultations are due to HPV-6/11.

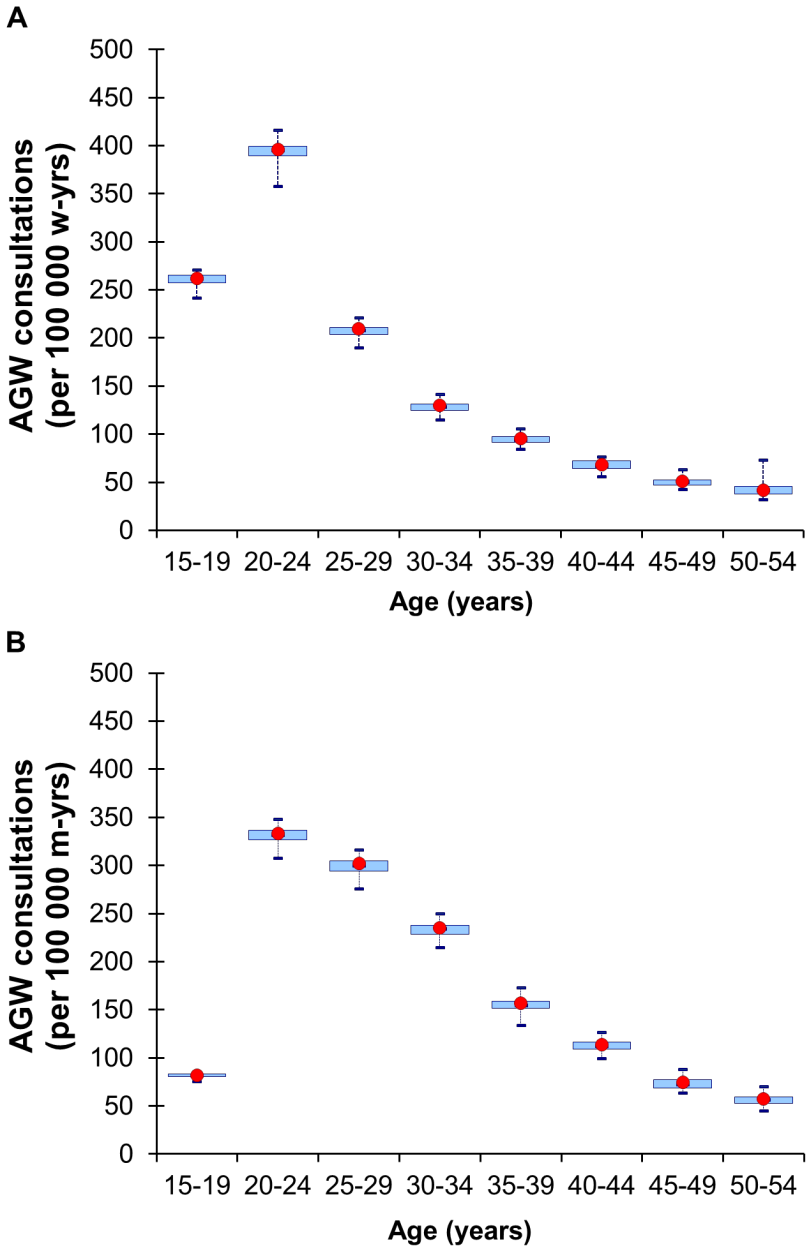


Figure A45. Anogenital warts consultation rates A) women and B) men. Box plots represent the minimum, maximum and the 25, 50 and 75th percentiles of the model predictions generated by the posterior parameter sets. Dots represent observed data [22].

2.3.6 Examples of fit to other HPV-related cancers

The model fits the age-, gender and type-specific incidence of cervical adenocarcinoma, and cancers of the vulva, vagina, anus, penis, and oropharynx in Canada[23-26].

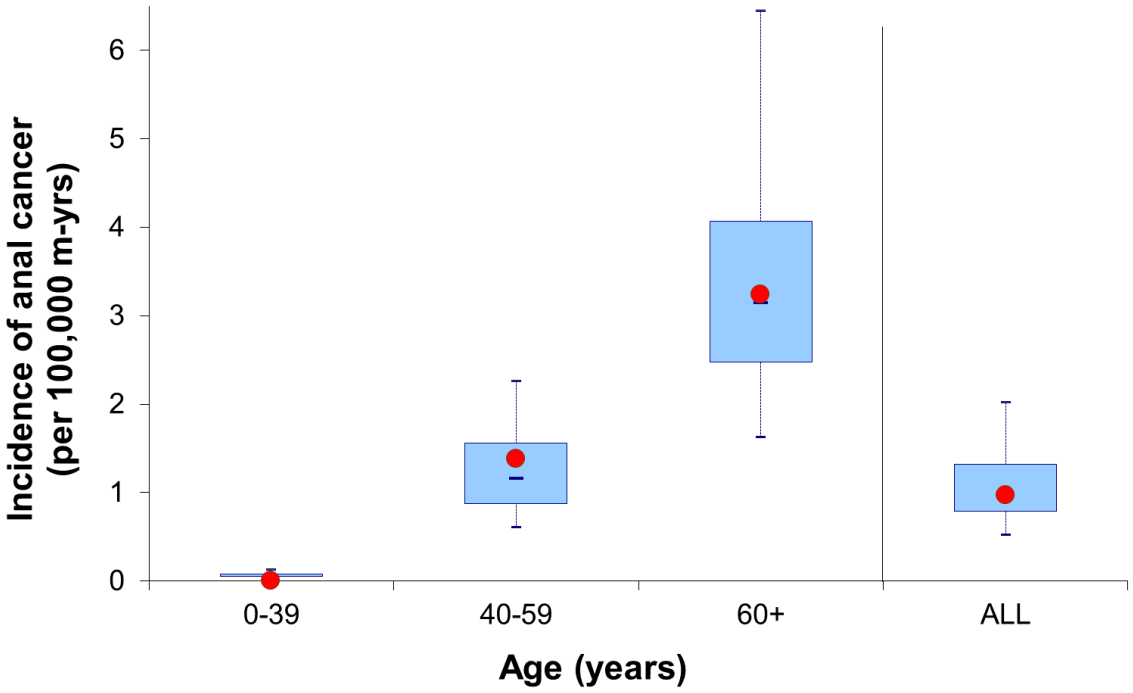


Figure A46. Rates of anal cancers positive for HPV in males. Box plots represent the minimum, maximum and the 25, 50 and 75th percentiles of the model predictions generated by the posterior parameter sets. Dots represent observed data[23].

2.4 Model validation

Model fit was cross-validated by comparing model predictions using the posterior parameter sets with observed data not used during the fitting procedure. Figure A47 and A46-A47 illustrate the fit to sexual behavior and type distribution data, respectively.

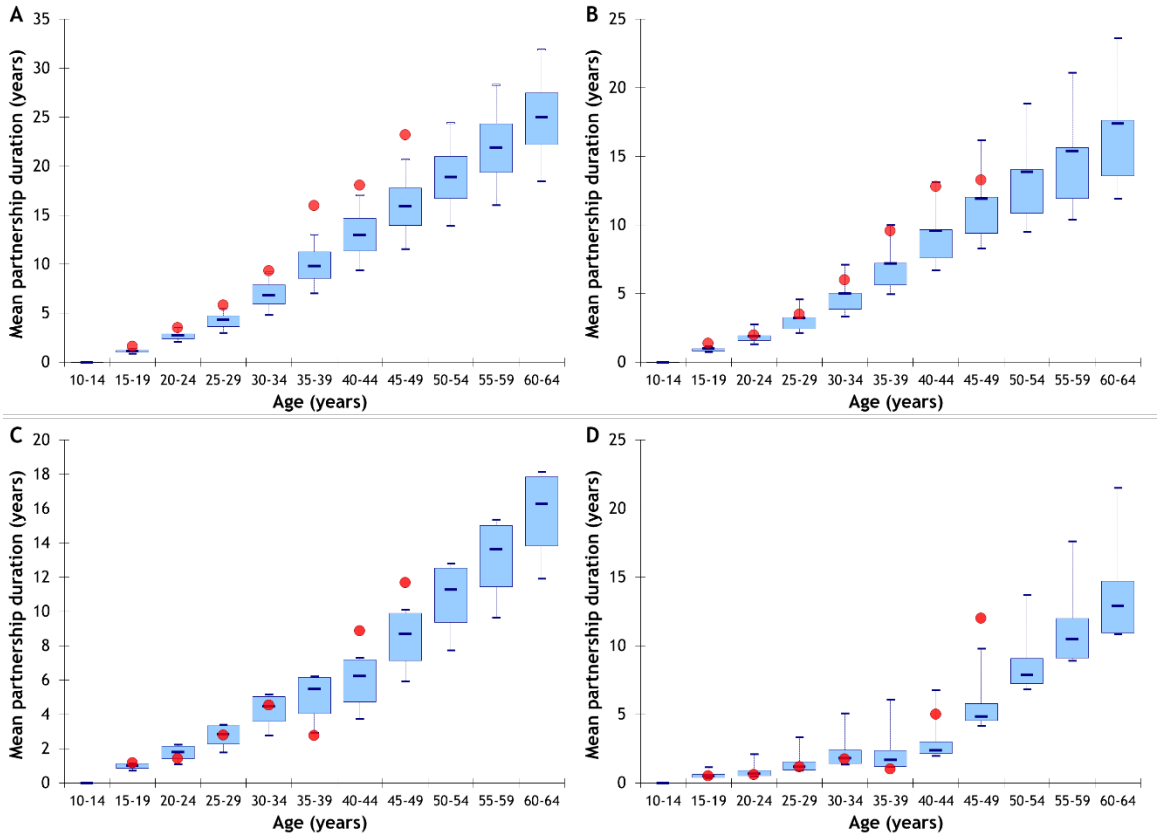


Figure A47. Mean partnership duration in women in level of sexual activity A) $l = 0$, B) $l = 1$ and C) $l = 2$, and D) $l = 3$. Box plots represent the minimum, maximum and the 25, 50 and 75th percentiles of the model predictions generated by the posterior parameter sets. Dots represent observed data[28,29].

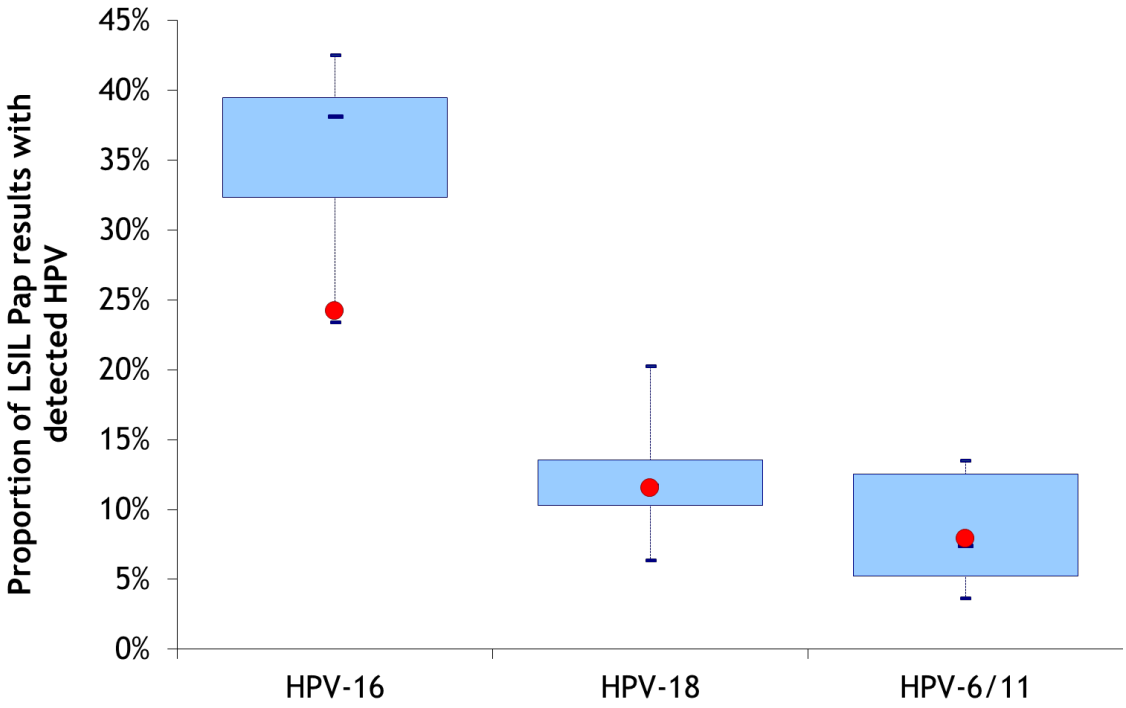


Figure A48. Proportion of LSIL Pap results with detected HPV-16, HPV-18 and HPV-6/11. Box plots represent the minimum, maximum and the 25, 50 and 75th percentiles of the model predictions generated by the posterior parameter sets. Dots represent observed data[66].

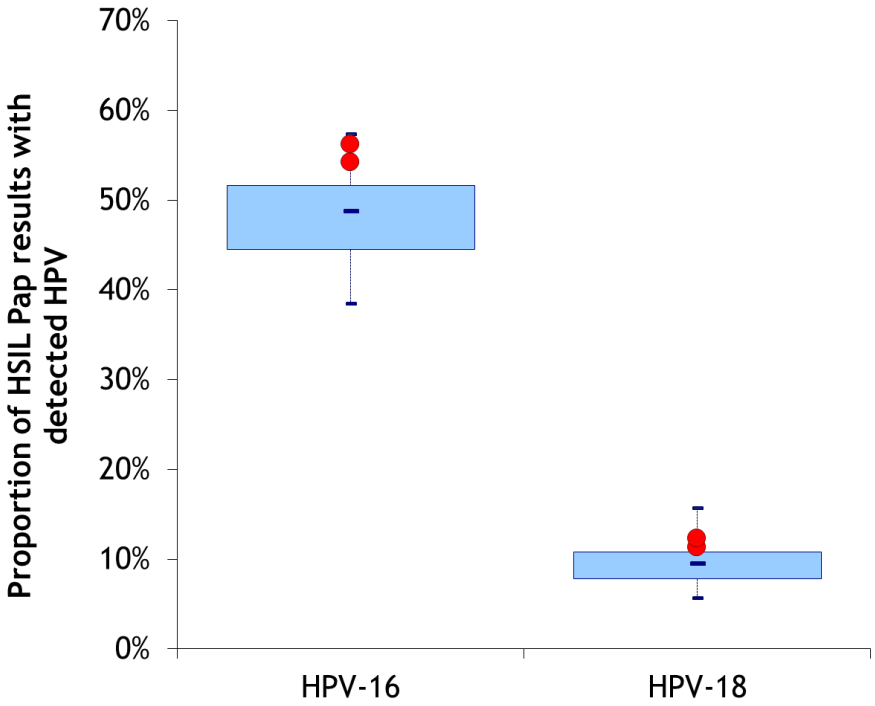


Figure A49. Proportion of HSIL Pap results with detected HPV-16 and HPV-18. Box plots represent the minimum, maximum and the 25, 50 and 75th percentiles of the model predictions generated by the posterior parameter sets. Dots represent the minimum and maximum values of the observed data [67,68].

2.5 Model predictive validation

We used the posterior parameter sets to produce model predictions of HPV quadrivalent vaccination impact on AGW consultations that were compared with post-vaccination surveillance data in Australia[69]. We modeled vaccination coverage using the observed age-specific vaccine uptake rates of HPV vaccine in Australia from 2007 to 2012[70]. Vaccine efficacy against infection is assumed to be 95%[71]. Figure A50 illustrates the fit to AGW consultations incidence in Australia following start of vaccination.

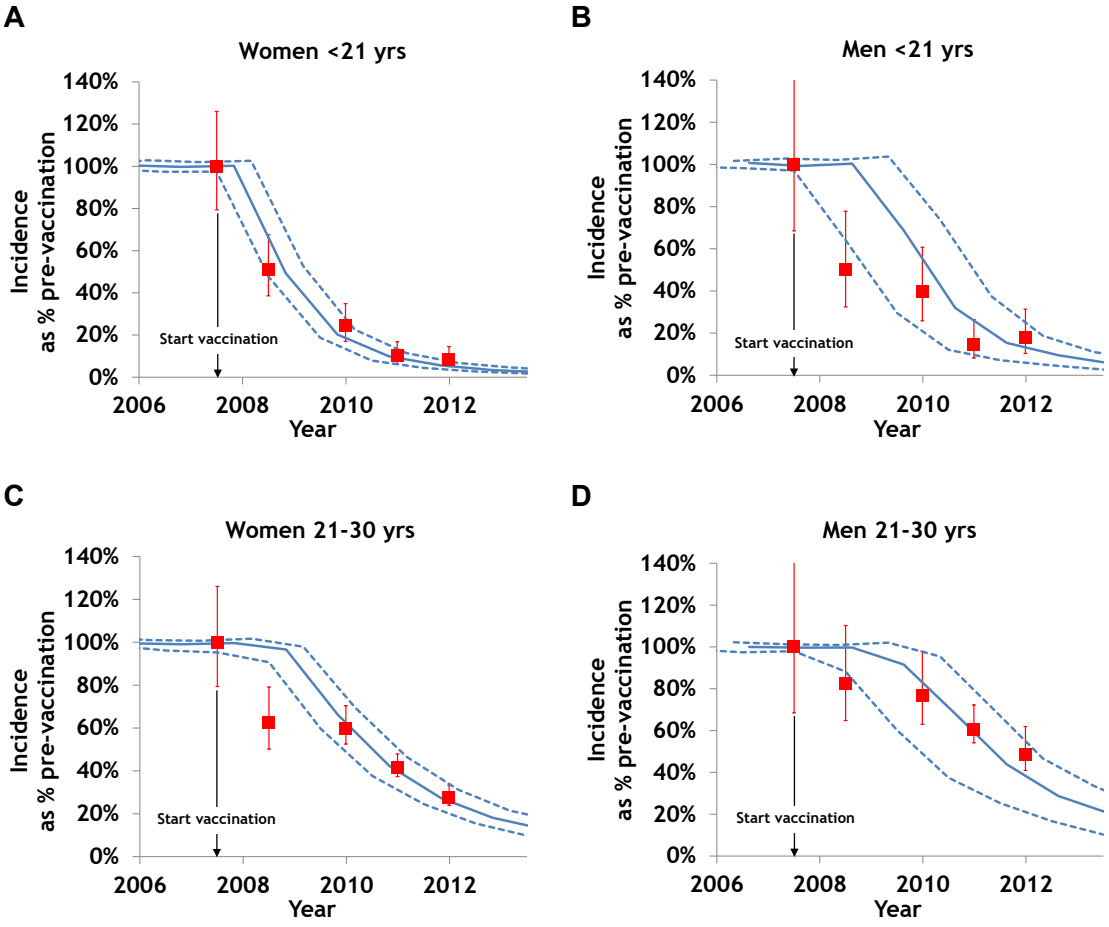
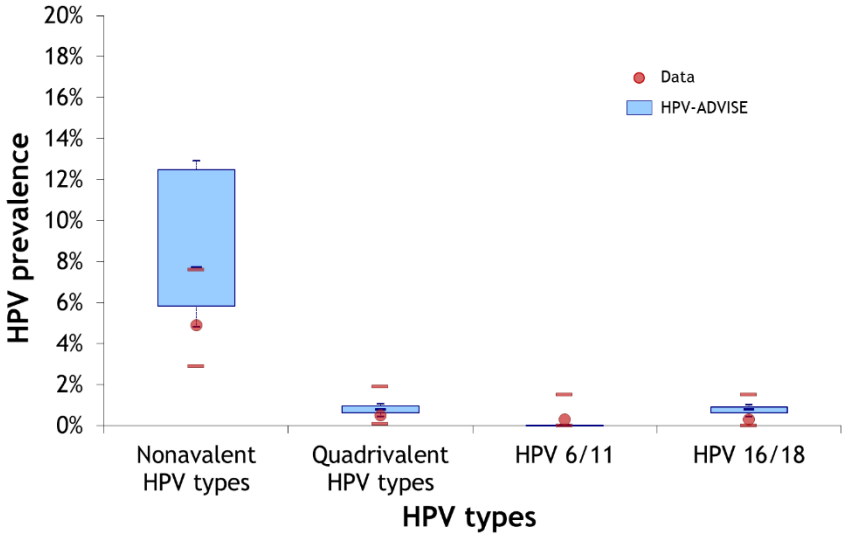


Figure A50. Incidence of anogenital wart consultations following start of vaccination in Australia as percentage of pre-vaccination incidence A) Women less than 21 years-old; **B)** Men less than 21 years-old; **C)** Women from 21 to 30 years of age; and **D)** Men from 21 to 30 years of age. Red squares with bars represent surveillance data with 95% confidence interval. Solid and dotted blue lines represent the median, and 10th and 90th percentiles of the model predictions.

A) HPV prevalence by grouped types in 2020-2022



B) HPV-16/18 prevalence over time

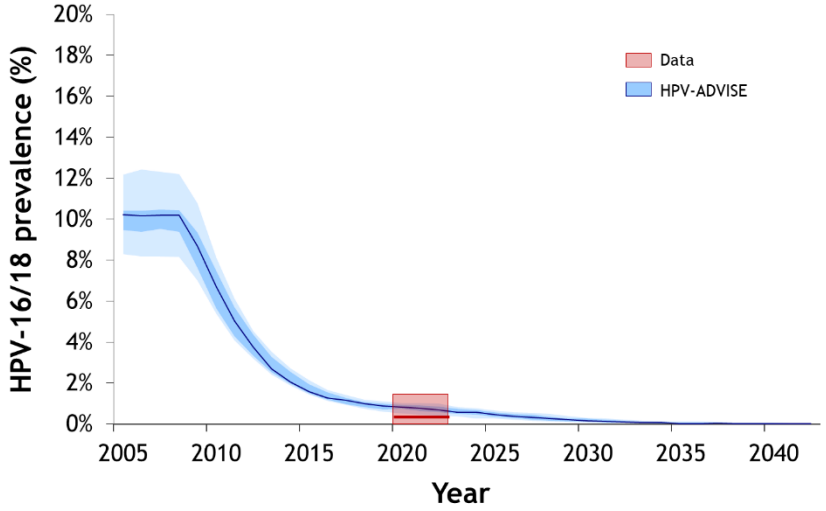


Figure A51. Comparison of model projections to post-vaccination data from Québec: HPV prevalence among unvaccinated males aged 16-20 years in 2020-2022. A) HPV prevalence by grouped types in 2020-2022, and **B)** HPV-16/18 prevalence over time. Data (red dots and their 95% confidence interval) obtained from a study conducted in the province of Quebec aiming to estimate HPV prevalence among unvaccinated males aged 16-20 years old.[72] Data were collected in 2020-2022 among unvaccinated cohorts of males aged 16 to 20 years. The age group was chosen as vaccination had not yet begun for males, 16-to-20-year-old females were vaccinated with the quadrivalent vaccine. Therefore, the change in HPV prevalence represent herd effect from females-only vaccination. Boxplots in Panel A, and solid line and shaded areas in Panel B represent the median, and 10th, 25th, 75th and 90th percentiles of HPV-ADVISE projections using 50 parameter sets. Four-valent HPV vaccine types include HPV-6/11/16/18, 9-valent HPV vaccine types include HPV-6/11/16/18/31/33/45/52/58.

2.6 Target definition

A prior parameter set is qualified as producing a ‘‘good fit”, and included as a posterior parameter set, if the associated model predictions fall simultaneously within pre-specified targets (ranges) of the sexual behavior, screening and epidemiological data defined in Table A1. The lower and upper bounds of these ranges are built based on target values, ξ, as follows:

$$\text{Lower bound} = \min_j \left(O_{i,g,a,l} \right) - \xi \tag{2.6}$$

$$\text{Upper bound} = \max_j \left(O_{i,g,a,l} \right) + \xi$$

Where i represents the data source and $\min_i (\cdot)$ takes the minimum value of all data sources for a specific data point $O_{i,g,a,l}$

The target values are defined as follows:

$$\xi_l = f \cdot \max_{i,a} \left(O_{i,a,l} \right) \tag{2.7}$$

Where $\max_{i,a} (\cdot)$ takes the maximum value over age of all data sources and $f = 0.5$, except for type distribution targets where $f = 0.2$.

2.7 List of symbols

Table A26. List of symbols.

Symbol	Units	Definition
Θ_i	(-)	i^{th} individual. Defined as the following individual state vector: $\Theta_i = \left(g, l, u, h^{\tau}, s, S; a\right)$ where $i = 1, 2, \ldots, N$
N	(#)	Number of individuals
e	(-)	The index e refers to a particular event (or change) in the state of an individual (e.g. death, infection, partnership formation). This index takes the following values: $e = 1, 2, \ldots, n_e$ where n_e is the total number of events and $e = 0$ refers to the null event.
a	(year)	Age
l	(-)	Level of sexual activity: $l \in \{0, 1, 2, 3\}$
g	(-)	Gender $g = 1$: female $g = 2$: male
h^{τ}	(-)	Health states $h = 0$: susceptible $h = 1$: infected $h = 2$: naturally immune $h = 3$: vaccine immune to the particular HPV type τ
τ	(-)	HPV type $\tau \in$ $\{16,18,6,11,31,33,45,52,58,35,39,51,56,59,66,68,73,82\}$
s	(-)	Partnership status $s = 0$: single $s = 1$: stable partnership $s = 2$: casual partnership
u	(-)	Sexual debut $u = 0$: not sexually active $u = 1$: sexually active
S	(-)	Screening behaviour levels $S \in \{0, 1, 2, 3, 4\}$)
$\mu_g(a)$	(per person-year)	Death rates with respect to age a, for a given gender g.
η	(per person-year)	Rates of entry in the population (at 10 years of age).
$\varphi_l(a)$	(per woman-year)	Rates of onset of sexual activity in females with respect to age a, for a given level of sexual activity l.

Φ_l	(%)	Percentage of individuals in each sexual activity level l.
$\varsigma_l(a)$	(per woman-year)	Partnership formation rates in single females with respect to age a, for a given level of sexual activity l.
$\theta_{g,l}(a)$	(per person-year)	Partner acquisition rates with respect to age a, for a given level of sexual activity l.
$\psi_l(a)$	(%)	Percentage of partnerships that lead to a stable partnership with respect to the age a and level of sexual activity l of the female partner.
$\Psi_l(a)$	(%)	Percentage of women in stable partnerships with respect to age a, for a given sexual activity level l.
$\mathbf{\Omega} = [\Omega_{al,a'l'}]$	(-)	Global mixing matrix. Represents the probability that a female of age a and level of sexual activity l will choose a male of age a' and level of sexual activity l'.
$\mathbf{\Gamma} = [\Gamma_{l,l',g}]$	(-)	Mixing by level of sexual activity. Represents the probability that an individual of sex g and level of sexual activity l forms a partnership with someone of the opposite sex in level of sexual activity l'.
$\mathbf{\Lambda} = [\Lambda_{a,a',l,g}]$	(-)	Mixing by age. Represents the probability that an individual of sex g in age group a and sexual activity level l forms a partnership with someone of the opposite sex in age group a'.
κ	(-)	Assortative degree
$\mathbf{W}$	(-)	Preference matrix $W_{l,l',g} = \begin{cases} \kappa, \text{ if } l = l' \\ 1, \text{ if } l \neq l' \end{cases}$
$\sigma_l(a)$	(per woman-year)	Rates of partnership separation in females with respect to age a, for a given level of sexual activity l.
ω	(# acts per week)	Frequency of sex acts per week in stable partnerships
$d_l(a)$	(year)	Duration of stable partnerships with respect to age a, for a given level of sexual activity l.
C	(# acts)	Number of sex acts in casual partnerships
β_g^τ	(-)	Per-act transmission probability, for a given HPV type τ and gender g (i.e. $g = 1$ and 2 for male-to-female and female-to-male transmission, respectively).
$\gamma_g^\tau(a)$	(per infection-year)	Clearance rates of a given HPV type τ, depending on the gender g and age a of the host.
M_g	(-)	Probability of developing lifelong natural immunity, for a given gender g.
Δt	(hours)	Time step
$\rho_{g,l,u,s,S}^{e,h^\tau}(a)$	(per person-year)	Rates of occurrence of event e for individuals in risk category $(g,l,u,s,S;h^\tau;a)$

$X^{h^\tau}_{g,l,u,s,S}(a;t_{k-1},t_k)$	(#)	Number of individuals in a given health state h^τ and risk categories $\{g,l,u,s,S,a\}$ during time interval $\Delta t_k = t_k - t_{k-1}$
$I^\tau_{g,l}(a;t_{k-1},t_k)$	(#)	Number of new type-specific infections by gender g, age a and level of sexual activity l during time interval Δt_k
VA	(year)	Vaccination age
VC	(%)	Vaccine coverage
VD	(year)	Vaccine duration
VE	(%)	Vaccine efficacy (degree of protection per act)

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